The NEW ENGLAND
JOURNAL of MEDICINE

Notable Articles of 2024

A collection of articles from the *New England Journal of Medicine* selected by NEJM editors

Nivolumab
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Vinblastine
Dacarbazine
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The NEW ENGLAND
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December 2024

Dear Reader,

In December, as our attentions turn to the new year ahead, I always find it interesting to reflect on the studies we've published in the past year and evaluate their contribution to the ever-evolving practice of medicine.

New interventions include a vaccine that offers protection from Dengue, a therapy that could prevent transmission of HIV in women, a CRISPR-based therapy for hereditary angioedema, a new class of therapy for cardiomyopathy associated with transthyretin amyloidosis, and a method to prevent or reverse cancer cachexia.

This year we've also seen many new applications for existing drugs, including GLP-1RAs, for improved treatment in heart failure with preserved ejection fraction, CKD, and MASH with liver fibrosis. Another trial showed efficacy for existing treatment for MASH. For the first time, a study showed that a mineralocorticoid receptor antagonist (MRA) improved cardiovascular outcomes in heart failure and preserved or mildly reduced ejection fraction. Results in two separate studies offered strong support for an enhanced chemotherapy regimen in patients with early-stage triple-negative breast cancer, and patients with advanced Hodgkin's lymphoma.

We published the first trial to show that a monoclonal antibody to IgE can effectively improve tolerance of multiple foods among children with multiple food allergies. And, new information on consciousness in comatose patients revealed that 25% of patients had verifiable responsiveness.

On behalf of the editorial team, we hope you enjoy reading this collection of studies that we believe stand out among the year's most notable and impactful in clinical medicine. As we look forward to the new year, we at the Journal remain committed to publishing only the most valuable, peer-reviewed studies — studies you can trust to inform and guide the care you provide to your patients. My sense is that we are now receiving more exciting manuscripts than in the last several years so I'm looking forward to a great 2025. I hope you travel along with us.

Sincerely,
Eric J. Rubin, M.D., Ph.D.
Editor-in-Chief, *New England Journal of Medicine*

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2024 VOL. 390 NO. 5

Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults

E.G. Kallás, M.A.T. Cintra, J.A. Moreira, E.G. Patiño, P.E. Braga, J.C.V. Tenório, V. Infante, R. Palacios, M.V.G. de Lacerda, D.B. Pereira, A.J. da Fonseca, R.Q. Gurgel, I.C.-B. Coelho, C.J.F. Fontes, E.T.A. Marques, G.A.S. Romero, M.M. Teixeira, A.M. Siqueira, A.M.P. Barral, V.S. Boaventura, F. Ramos, E. Elias Júnior, J. Cassio de Moraes, D.T. Covas, J. Kalil, A.R. Precioso, S.S. Whitehead, A. Esteves-Jaramillo, T. Shekar, J.-J. Lee, J. Macey, S.G. Kelner, B.-A.G. Coller, F.C. Boulos, and M.L. Nogueira

ABSTRACT

BACKGROUND

Butantan–Dengue Vaccine (Butantan-DV) is an investigational, single-dose, live, attenuated, tetravalent vaccine against dengue disease, but data on its overall efficacy are needed.

METHODS

In an ongoing phase 3, double-blind trial in Brazil, we randomly assigned participants to receive Butantan-DV or placebo, with stratification according to age (2 to 6 years, 7 to 17 years, and 18 to 59 years); 5 years of follow-up is planned. The objectives of the trial were to evaluate overall vaccine efficacy against symptomatic, virologically confirmed dengue of any serotype occurring more than 28 days after vaccination (the primary efficacy end point), regardless of serostatus at baseline, and to describe safety up to day 21 (the primary safety end point). Here, vaccine efficacy was assessed on the basis of 2 years of follow-up for each participant, and safety as solicited vaccine-related adverse events reported up to day 21 after injection. Key secondary objectives were to assess vaccine efficacy among participants according to dengue serostatus at baseline and according to the dengue viral serotype; efficacy according to age was also assessed.

RESULTS

Over a 3-year enrollment period, 16,235 participants received either Butantan-DV (10,259 participants) or placebo (5976 participants). The overall 2-year vaccine efficacy was 79.6% (95% confidence interval [CI], 70.0 to 86.3) — 73.6% (95% CI, 57.6 to 83.7) among participants with no evidence of previous dengue exposure and 89.2% (95% CI, 77.6 to 95.6) among those with a history of exposure. Vaccine efficacy was 80.1% (95% CI, 66.0 to 88.4) among participants 2 to 6 years of age, 77.8% (95% CI, 55.6 to 89.6) among those 7 to 17 years of age, and 90.0% (95% CI, 68.2 to 97.5) among those 18 to 59 years of age. Efficacy against DENV-1 was 89.5% (95% CI, 78.7 to 95.0) and against DENV-2 was 69.6% (95% CI, 50.8 to 81.5). DENV-3 and DENV-4 were not detected during the follow-up period. Solicited systemic vaccine- or placebo-related adverse events within 21 days after injection were more common with Butantan-DV than with placebo (58.3% of participants, vs. 45.6%).

CONCLUSIONS

A single dose of Butantan-DV prevented symptomatic DENV-1 and DENV-2, regardless of dengue serostatus at baseline, through 2 years of follow-up. (Funded by Instituto Butantan and others; DEN-03-IB ClinicalTrials.gov number, NCT02406729, and WHO ICTRP number, U1111-1168-8679.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Castro Boulos can be contacted at fernanda.boulos@fundacaobutantan.org.br or at Instituto Butantan, Avenue Vital Brasil, 1500-Butantã, São Paulo, Brazil.

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RESEARCH SUMMARY

Live, Attenuated, Tetravalent Butantan–Dengue Vaccine in Children and Adults

Kallás EG et al. DOI: 10.1056/NEJMoa2301790

CLINICAL PROBLEM

Two tetravalent, live, attenuated dengue virus (DENV) vaccines are currently licensed in selected countries; however, a single-dose vaccine that is indicated for a broad age range and protects against all four DENV serotypes, without regard to dengue serostatus, is needed.

CLINICAL TRIAL

Design: An ongoing phase 3, double-blind, randomized, placebo-controlled trial conducted in Brazil assessed the efficacy and safety of a single-dose, live, attenuated, tetravalent vaccine candidate, Butantan–Dengue Vaccine (Butantan-DV), for prevention of symptomatic, virologically confirmed dengue in children, adolescents, and adults with or without previous dengue exposure.

Intervention: 16,235 participants 2 to 59 years of age were assigned in a 2:1 ratio to receive a single dose of Butantan-DV or placebo. In this prespecified analysis at 2 years of follow-up (of a projected 5-year follow-up), the primary end point was the incidence of symptomatic, virologically confirmed dengue >28 days after injection, regardless of previous exposure to dengue.

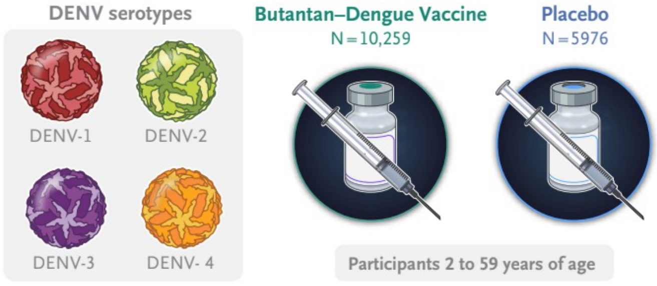
RESULTS

Efficacy: During 2 years of follow-up, fewer symptomatic cases of virologically confirmed dengue occurred in the vaccine group than in the placebo group.

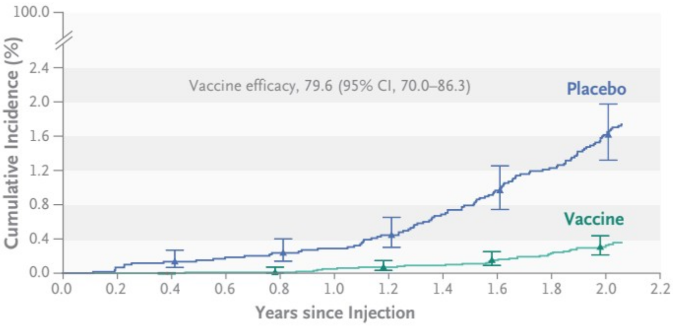
Safety: Within 21 days after injection, solicited systemic vaccine- or placebo-related adverse events — most often headache, fatigue, or rash — occurred more frequently in the vaccine group.

LIMITATIONS AND REMAINING QUESTIONS

- No DENV-3 or DENV-4 cases occurred, which precluded assessment of vaccine efficacy against these serotypes.
- No safety concerns were identified; careful follow-up through the planned 5 years will be important to confirm this finding.
- The effect of preexisting immunity from other flaviviruses (Zika virus or yellow fever) on subsequent DENV infection or Butantan-DV vaccination requires exploration.
- A low incidence of virologically confirmed dengue precluded meaningful analyses of vaccine efficacy against severe dengue.

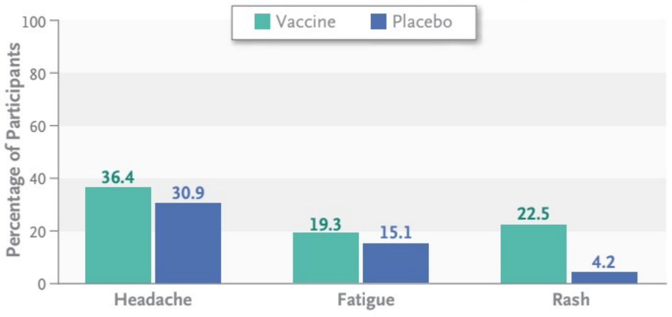


Symptomatic, Virologically Confirmed Dengue >28 Days after Injection



	Vaccine	Placebo
Estimated Incidence	0.17/100 person-yr at risk (95% CI, 0.12–0.24)	0.84/100 person-yr at risk (95% CI, 0.68–1.02)

Most Common Solicited Systemic Adverse Events ≤21 Days after Injection



CONCLUSIONS

In an ongoing phase 3 trial in Brazil, a single dose of Butantan-DV prevented symptomatic DENV-1 and DENV-2 in children and adults, regardless of dengue serostatus at baseline, through 2 years of follow-up.

EDITORIAL

Three Dengue Vaccines — What Now?

Scott B. Halstead, M.D.

In 2019, the four serotypes of the mosquito-borne dengue virus (DENV) caused an estimated 56 million cases of disease and 5000 to 40,000 deaths in a global swath of tropical and near-tropical countries, defying control and motivating the development of vaccines.[1] Outcomes of clinical trials of dengue vaccines are necessarily governed by the biologic and immunologic behavior of DENV in humans. Initial infection with any DENV serotype in persons who have not previously been infected with DENV typically results in at most mild-to-moderate febrile illnesses of short duration. These initial infections provide lifelong protection against reinfection with the same immunologic DENV serotype. Second heterotypic dengue infections occur in 12 sequences (e.g., DENV-1 then DENV-2, DENV-2 then DENV-3, etc.). Second infections are responsible for much of the spectrum of severe dengue illnesses worldwide. Severe dengue disease occurs only in rare cases during a third or fourth DENV infection. It is this two-infection protective immune status that fuels the development of dengue vaccines.

There is a red flag, however: when multi-DENV IgG antibodies are transferred to fetuses through the placenta, DENV infections in the newborns are prevented for weeks to months. However, when antibodies are catabolized to nonprotective levels, these infants may have antibody-enhanced DENV infections that result in severe disease, hospitalization, and death.[2] Nonneutralizing DENV IgG antibodies, whether acquired through infection or vaccine, are a universal risk factor for severe dengue among persons who do not have protective immunity. Unfortunately, there are no agreed-upon serologic criteria that identify protective immunity in persons who are thought to have had two or more DENV infections. This lack of an identified protective factor makes clinical trials of tetravalent dengue vaccines important learning experiences.

Nearly 50 years have passed since development of a tetravalent dengue vaccine was initiated at the Walter Reed Army Institute of Research. Since then, three fundamental discoveries have challenged the design of a dengue vaccine: antibody-dependent enhancement, the protective role of cellular immunity,[3] and the direct pathogenicity of dengue nonstructural protein 1 (NS1).[4] In order to provide a high level of protection, dengue vaccines should present a full array of structural and nonstructural antigens (including NS1) of all four DENV serotypes.

Efficacy trials involving three tetravalent dengue vaccines have been completed. Dengvaxia (Sanofi) is a yellow fever virus–derived vaccine integrated chimerically with the structural regions of the four DENV serotypes. The large, well-designed, multicountry clinical trial of three doses of Dengvaxia provided unexpected but informative results. Tetravalent neutralizing antibodies developed in nearly all vaccinees in the trial. Vaccinated seronegative participants had unexpected breakthrough DENV infections, including severe disease, with some cases leading to hospitalization for illness characterized by vascular permeability. Vaccinated seropositive participants were protected against breakthrough DENV illnesses.[5] The two-dose dengue vaccine, TAK-003, also known as Qdenga (Takeda), contains live, attenuated DENV-2 plus DENV-2 chimeras of the structural regions of DENV-1, DENV-3, and DENV-4. In clinical trials, there was one unequivocally positive outcome: vaccinated seronegative participants and seropositive participants were highly protected against DENV-2 disease. A serious limitation was the absence of DEN-4 infections. Moderate protection against DENV-1 disease was found in both seronegative participants and seropositive participants, and a suggestion of a higher frequency of hospitalization for DENV-3 disease among vaccinated seronegative participants.[6]

In this issue of the *Journal*, Kallás et al.[7] report the findings from their phase 3 trial of a single administration of Butantan-DV (Instituto Butantan), a tetravalent vaccine developed in a National Institute of Allergy and Infectious Diseases laboratory.[8] Between February 2016 and July 2019, one dose of Butantan-DV, containing full-length attenuated DENV-1, DENV-3, and DENV-4 plus a DENV-2–DENV-4 chimera, was administered to 10,259 children and adults at 16 sites in five geographical regions of Brazil; placebo was administered to 5976 children and adults. Vaccine efficacy against overt mild DENV-1 dengue disease was 96.8% and 85.6% among seropositive participants and seronegative participants, respectively, with modest efficacy against overt DENV-2 disease among 83.7% and 57.9%, respectively. On the basis of protection against DENV that was shown during preclinical testing of the analogous TV003 formulation developed by the National Institutes of Health, it was expected that a single dose of Butantan-DV would provide protective immunity against all four DENV serotypes.[9] The absence of cases of DENV-3 and DENV-4 undoubtedly is attributable to the introduction of Zika virus (ZIKV) to Brazil in 2015. The number of ZIKV infections exploded to epidemic proportions and was followed in both 2017 and 2018 by an 80% reduction in total dengue cases and deaths. Among the 270 participants who received vaccine or placebo in the current trial and in whom clinical dengue illnesses developed during the trial, none were severely ill or hospitalized. This is in stark contrast to the frequency of severe dengue or hospitalization of vaccinees and controls in clinical trials of Dengvaxia and TAK-003. ZIKV, a flavivirus, behaves antigenically like a fifth DENV. A person with monotypic DENV immunity who has been infected with ZIKV converts to the immune status of a person who has been infected with two DENV serotypes,[10] and there should be an unusually high prevalence of the antibody patterns associated with two DENV serotypes in the prevaccination serum samples of these persons. This possibility should be studied.

What now? The World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE) has recommended that persons 9 years of age or older with evidence of at least one previous DENV infection receive three doses of Dengvaxia. SAGE is considering recommending that persons 6 to 16 years of age in countries where DENV is highly endemic receive two doses of TAK-003 without restriction. Given the realities of the dimensions of the dengue pandemic in the 20th and 21st centuries, a highly effective, one-dose, tetravalent vaccine remains in high demand. Butantan-DV clinical trials should continue and, if possible, be expanded.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From Westwood, MA. Dr. Halstead is the founding director (retired) of the Pediatric Dengue Vaccine Initiative, International Vaccine Institute, Seoul, South Korea.

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The NEW ENGLAND JOURNAL of MEDICINE

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A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

S.A. Harrison, P. Bedossa, C.D. Guy, J.M. Schattenberg, R. Loomba, R. Taub, D. Labriola, S.E. Moussa, G.W. Neff, M.E. Rinella, Q.M. Anstee, M.F. Abdelmalek, Z. Younossi, S.J. Baum, S. Francque, M.R. Charlton, P.N. Newsome, N. Lanthier, I. Schiefke, A. Mangia, J.M. Pericàs, R. Patil, A.J. Sanyal, M. Noureddin, M.B. Bansal, N. Alkhouri, L. Castera, M. Rudraraju, and V. Ratziu, for the MAESTRO-NASH Investigators*

ABSTRACT

BACKGROUND

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with no approved treatment. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH with liver fibrosis.

METHODS

We are conducting an ongoing phase 3 trial involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

RESULTS

Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group). NASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group (P<0.001 for both comparisons with placebo). Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group (P<0.001 for both comparisons with placebo). The change in low-density lipoprotein cholesterol levels from baseline to week 24 was −13.6% in the 80-mg resmetirom group and −16.3% in the 100-mg resmetirom group, as compared with 0.1% in the placebo group (P<0.001 for both comparisons with placebo). Diarrhea and nausea were more frequent with resmetirom than with placebo. The incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group.

CONCLUSIONS

Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage. (Funded by Madrigal Pharmaceuticals; MAESTRO-NASH ClinicalTrials.gov number, NCT03900429.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Harrison can be contacted at sharrison@pinnacleresearch.com or at Pinnacle Clinical Research, 5109 Medical Dr., Suite 200, San Antonio, TX 78229.

*A complete list of the investigators in the MAESTRO-NASH trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was last updated on February 16, 2024, at NEJM.org.

N Engl J Med 2024;390:497-509.
DOI: 10.1056/NEJMoa2309000

A Quick Take is available at NEJM.org

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RESEARCH SUMMARY

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

CLINICAL PROBLEM

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease characterized by ≥5% hepatic steatosis with hepatocellular damage and inflammation. There are currently no approved pharmacologic treatments for NASH. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta–selective agonist in development for the treatment of NASH.

CLINICAL TRIAL

Design: An ongoing, phase 3, multinational, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of resmetirom in adults with biopsy-confirmed NASH and liver fibrosis.

Intervention: 966 patients with NASH and fibrosis of stage F1B, F2, or F3 were assigned in a 1:1:1 ratio to receive once-daily resmetirom (80 mg or 100 mg) or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by ≥1 stage with no worsening of the NAFLD activity score.

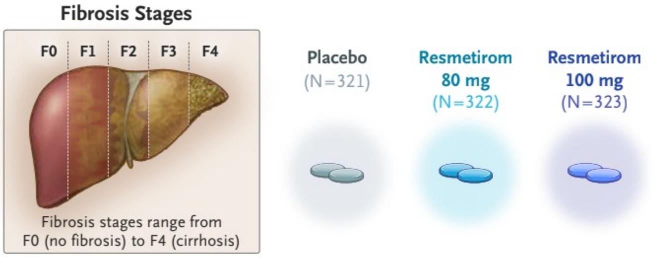
RESULTS

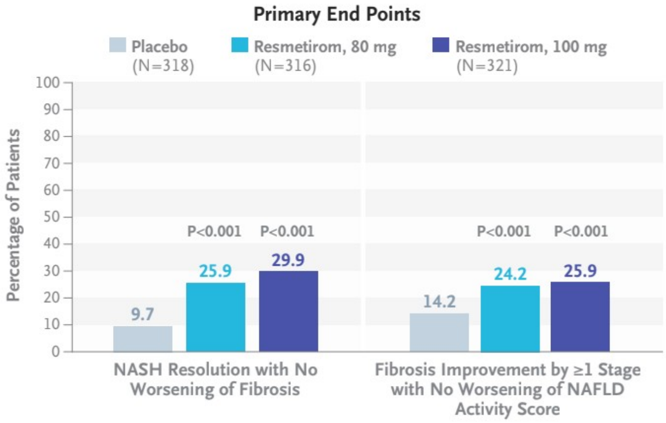
Efficacy: Among evaluable patients, both doses of resmetirom were superior to placebo with respect to the two primary end points.

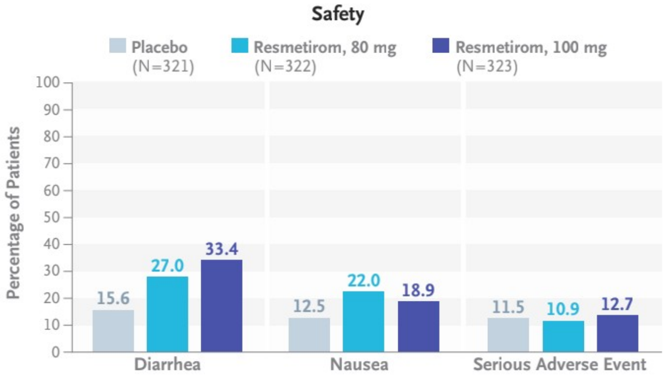
Safety: More than 90% of the patients in each group had adverse events, most of which were mild or moderate in severity. Diarrhea and nausea occurred more often with resmetirom than with placebo. The incidence of serious adverse events was similar among the groups.

LIMITATIONS AND REMAINING QUESTIONS

- The trial lacked clinical-outcomes data to correlate with the histologic data. The trial is planned to continue to 54 months to evaluate liver-related outcomes, including progression to cirrhosis.
- Almost 90% of the participants were White, which limits the generalizability of the findings to other racial or ethnic groups.


Fibrosis Stages
F0
F1
F2
F3
F4
Fibrosis stages range from F0 (no fibrosis) to F4 (cirrhosis)
Placebo (N=321)
Resmetirom 80 mg (N=322)
Resmetirom 100 mg (N=323)





CONCLUSIONS

In patients with NASH and liver fibrosis, once-daily treatment with resmetirom was superior to placebo with respect to NASH resolution and fibrosis improvement by ≥1 stage at 52 weeks of follow-up.

EDITORIAL

Selective Agonists of Thyroid Hormone Receptor Beta for the Treatment of NASH

Kenneth Cusi, M.D.

Nonalcoholic fatty liver disease (NAFLD) is a common condition associated with cirrhosis and hepatocellular carcinoma, affecting approximately 70% of people with obesity or type 2 diabetes.[1] In the absence of approved pharmacotherapies, current guidelines[1-3] recommend reversing nonalcoholic steatohepatitis (NASH) by targeting obesity or type 2 diabetes, either with weight loss from lifestyle intervention and the use of glucagon-like peptide-1 (GLP-1) receptor agonists or with the treatment of type 2 diabetes with an insulin sensitizer such as pioglitazone.[1-3] Thyroid hormone modulates hepatic glucose and lipid metabolism.[1] Hypothyroidism is associated with steatosis, although its role in steatohepatitis is difficult to separate from that of insulin resistance, obesity, and type 2 diabetes.[4-6] Thyroid hormone receptor beta (THR-β) agonists reverse steatosis by many mechanisms, including improving hepatic conversion of T4 to T3 and enhancing mitochondrial function.[5,6] Selective agonists of THR-β, such as resmetirom, activate the major thyroid hormone receptor isoform in the liver (THR-β, also predominant in the kidneys, pituitary gland, and brain) while believed to avoid thyroid hormone receptor alpha (THR-α)–related side effects in the heart and bones.

In this issue of the *Journal*, Harrison et al.[7] report the week 52 results of the ongoing phase 3 MAESTRO-NASH trial, in which 966 adults with NASH and liver fibrosis were randomly assigned to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. Both doses of resmetirom were superior to placebo with respect to the two primary end points: NASH resolution with no worsening of fibrosis (in 25.9 to 29.9% of patients receiving resmetirom vs. 9.7% of those receiving placebo) and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score (in 24.2 to 25.9% of patients receiving resmetirom vs. 14.2% of those receiving placebo). Resmetirom also ameliorated atherogenic dyslipidemia. It had overall neutral effects on body weight, insulin resistance, glycemia, heart rate, and blood pressure. The drug had an acceptable adverse-event profile, with only nausea, vomiting, and diarrhea occurring more frequently with resmetirom than with placebo. No increase in endocrine adverse events was reported.

Among the patients with available data, resmetirom markedly increased sex hormone–binding globulin levels and increased levels of total estradiol and testosterone. Elevations in sex hormone–binding globulin levels indicate THR-β engagement and are associated with treatment response. Although free testosterone levels were unchanged (free estradiol levels were not reported), it is unclear whether long-term elevations in sex hormone–binding globulin levels may alter delivery of testosterone to target tissues and promote clinically significant gonadal axis changes, because the binding dynamics of testosterone to its binding proteins are complex and incompletely understood.[8] Proper clinical monitoring and accurate measurement of free hormone levels by the reference-standard equilibrium dialysis method would be recommended.[8] Treatment affected the pituitary–thyroid hormone axis, with prohormone free T4 levels decreasing by approximately 17 to 21% and mean thyrotropin levels also decreasing. Although it was reassuring that mean plasma free T3 levels remained normal, further information on individual cases

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within the lower range of normal (or below normal) would be informative.

The long-term significance of the above hormonal changes, if any, is unclear. Theoretically, suppression of pituitary thyrotropin secretion by THR-β agonists could promote a hypothyroid state in tissues not targeted by the agent. Diagnosing mild hypothyroidism is difficult in terms of attributing symptoms to the thyroid dysfunction[9] and even more challenging when the thyrotropin level is normal or low with subnormal serum free T4 levels,[10] as with selective agonists of THR-β. Careful case finding during follow-up is needed, including endocrine-specific history taking, dedicated questionnaires, and reliable periodic free hormone measurements. With respect to bone metabolism, selective agonists of THR-β are considered to be safe overall because bone loss is more closely related to long-term THR-α activation.[5,6] However, THR-β appears to also play an important role in bone metabolism.[11] In the subgroup of patients reported (23%), there was no shift in bone mineral density (BMD) T-score risk category. Data of value in the future would be vitamin D levels (vitamin D deficiency may develop in patients with persistent diarrhea), levels of biomarkers of bone turnover, and quantitative changes in BMD.

Taken together, these results are encouraging to the field. Both NASH resolution and fibrosis improvement were more likely with resmetirom than with placebo. If conditional approval is given by the Food and Drug Administration, it may boost guideline recommendations to screen in primary care persons at high risk for NASH, especially to identify those with stage F2 or higher fibrosis (known as "at risk" NASH).[1-3] However, the trial also highlights the challenging nature of the disease. Although resmetirom treatment was successful, the placebo-subtracted effect of resmetirom was overall modest (16.4 to 20.7 percentage points for NASH resolution and 10.2 to 11.8 percentage points for fibrosis), which means that approximately 2 of 10 patients treated will have NASH resolution and approximately 1 of 10 patients treated will have fibrosis improvement. Thus, most patients will need combination therapy with agents for obesity and type 2 diabetes recommended in guidelines (GLP-1 receptor agonists or pioglitazone).[1-3] If resmetirom is approved to treat F2 to F3 (moderate to advanced)) fibrosis, it is speculated that it will be a costly medication. How would resmetirom be used among less expensive medications that are effective for NASH and recommended in current guidelines[1-3] for obesity or type 2 diabetes? In the United States, at least 11.6 million people have NASH, and this figure is expected to nearly double during the next 15 years.[12] The estimated prevalence of stage F2 or F3 fibrosis among patients with type 2 diabetes (a population with the highest risk of cirrhosis) is 12 to 15%,[13,14] which means 4 to 5 million potential candidates for treatment just in the United States. The large number of person needing treatment will open a debate about treatment access and about how to best monitor treatment response and when to discontinue resmetirom in patients who do not have a response in order to avoid futile long-term therapy.

The 52-week results of this ongoing clinical trial are a step forward that brings hope to a field in desperate need of new therapies. They also create new management dilemmas and renew a sense of urgency conveyed in current guidelines to screen in primary care and endocrine settings for patients who may benefit from available and future treatments.[1-3] Resmetirom appeared safe overall, although careful surveillance to detect early endocrine disease that is related to potential thyroid, gonadal, or bone disease appears warranted to avoid any potential risks from long-term treatment. Definitive answers await the long-term safety and efficacy results of this ongoing 54-month trial.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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ORIGINAL ARTICLE

Omalizumab for the Treatment of Multiple Food Allergies

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ABSTRACT

BACKGROUND

Food allergies are common and are associated with substantial morbidity; the only approved treatment is oral immunotherapy for peanut allergy.

METHODS

In this trial, we assessed whether omalizumab, a monoclonal anti-IgE antibody, would be effective and safe as monotherapy in patients with multiple food allergies. Persons 1 to 55 years of age who were allergic to peanuts and at least two other trial-specified foods (cashew, milk, egg, walnut, wheat, and hazelnut) were screened. Inclusion required a reaction to a food challenge of 100 mg or less of peanut protein and 300 mg or less of the two other foods. Participants were randomly assigned, in a 2:1 ratio, to receive omalizumab or placebo administered subcutaneously (with the dose based on weight and IgE levels) every 2 to 4 weeks for 16 to 20 weeks, after which the challenges were repeated. The primary end point was ingestion of peanut protein in a single dose of 600 mg or more without dose-limiting symptoms. The three key secondary end points were the consumption of cashew, of milk, and of egg in single doses of at least 1000 mg each without dose-limiting symptoms. The first 60 participants (59 of whom were children or adolescents) who completed this first stage were enrolled in a 24-week open-label extension.

RESULTS

Of the 462 persons who were screened, 180 underwent randomization. The analysis population consisted of the 177 children and adolescents (1 to 17 years of age). A total of 79 of the 118 participants (67%) receiving omalizumab met the primary end-point criteria, as compared with 4 of the 59 participants (7%) receiving placebo (P<0.001). Results for the key secondary end points were consistent with those of the primary end point (cashew, 41% vs. 3%; milk, 66% vs. 10%; egg, 67% vs. 0%; P<0.001 for all comparisons). Safety end points did not differ between the groups, aside from more injection-site reactions in the omalizumab group.

CONCLUSIONS

In persons as young as 1 year of age with multiple food allergies, omalizumab treatment for 16 weeks was superior to placebo in increasing the reaction threshold for peanut and other common food allergens. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT03881696.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Wood can be contacted at rwood@jhmi.edu or at the Department of Pediatrics, Johns Hopkins University School of Medicine, 600 North Wolfe St., Baltimore, MD 21287.

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RESEARCH SUMMARY

Omalizumab for the Treatment of Multiple Food Allergies

Wood RA et al. DOI: 10.1056/NEJMoa2312382

CLINICAL PROBLEM

Food allergy affects up to 8% of children and 10% of adults in the United States, and a large percentage of people with food allergies are allergic to multiple foods. Because management has relied on food avoidance and emergency treatment in cases of accidental exposure, quality of life is affected. Omalizumab, a monoclonal anti-IgE antibody, holds promise as a monotherapy for people with multiple food allergies.

CLINICAL TRIAL

Design: A phase 3, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of omalizumab for patients with multiple food allergies, including peanut allergy.

Intervention: 177 children and adolescents 1 to 17 years of age who were allergic to peanuts (i.e., had food challenge reactivity to ≤100 mg of peanut protein) and at least two other protocol-specified foods (food challenge reactivity to ≤300 mg of cashew, egg, milk, walnut, wheat, or hazelnut) were assigned, in a 2:1 ratio, to receive subcutaneous omalizumab or placebo every 2 to 4 weeks for 16 to 20 weeks, after which the food challenges were repeated. The primary end point was consumption of a single dose of ≥600 mg of peanut protein without dose-limiting symptoms.

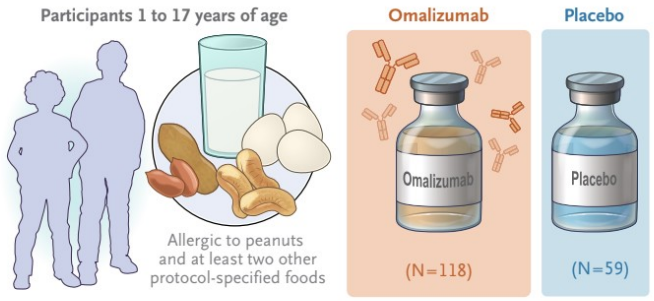
RESULTS

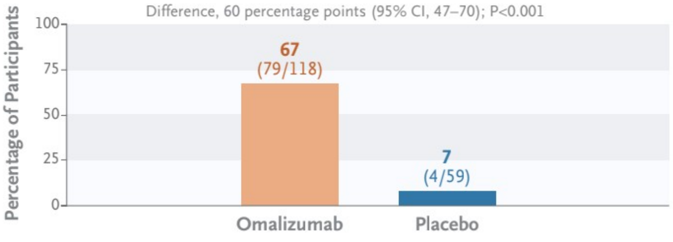
Efficacy: The percentage of participants who were able to consume ≥600 mg of peanut protein without dose-limiting symptoms was nearly 10 times higher in the omalizumab group than in the placebo group. Key secondary end points (the consumption of cashew, egg, or milk at prespecified threshold doses) also favored omalizumab.

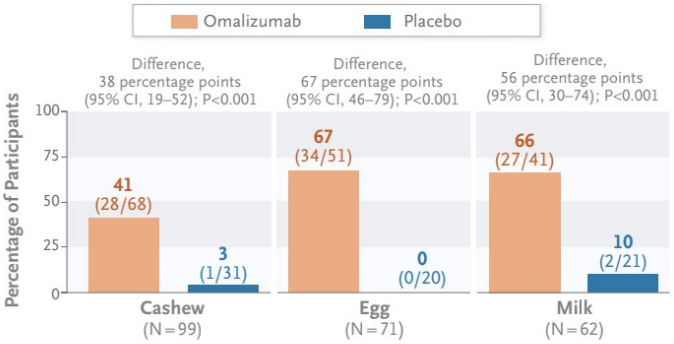
Safety: The incidence of adverse events was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- The cohort comprised mostly non-Hispanic and White children, which limits the generalizability of the findings.
- Patients with high baseline IgE levels were excluded.


Participants 1 to 17 years of age
Allergic to peanuts and at least two other protocol-specified foods
Omalizumab
Omalizumab
(N=118)
Placebo
Placebo
(N=59)


Consumption of ≥600 mg Peanut without Dose-Limiting Symptoms


Consumption of ≥1000 mg without Dose-Limiting Symptoms

CONCLUSIONS

In children as young as 1 year of age with multiple food allergies, including peanut allergy, omalizumab was superior to placebo in increasing the reaction threshold for peanut and other common food allergens.

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EDITORIAL

Options for Multiple Food Allergies — Food Avoidance or Pharmacologic Treatment?

Gary W.K. Wong, M.D.

Food allergy is common, affecting up to 8% of children and 10% of adults in the United States.[1,2] Hospital admission data for food-induced anaphylaxis have shown a clear increasing trend in the United States.[3] Food avoidance and use of rescue treatment if accidental exposure occurs are the only advice options we provide. Various forms of immunotherapy for treating food allergy have been investigated in the past decade. However, adverse reactions including anaphylaxis were found to be very common among patients receiving oral immunotherapy for food allergy.[4] Therefore, patients with severe food allergy, especially those who are allergic to multiple foods, have a substantial need for effective and safe treatments.

The concept of using anti-IgE antibody to protect patients with severe food allergy is not new. A randomized trial published in the *Journal* 20 years ago showed that the use of a humanized IgG1 monoclonal antibody, TNX-901, could significantly increase the threshold of reaction in patients with peanut allergy.[5] However, this drug never made it to market for clinical use. Since then, a similar antibody, omalizumab, has been tested and licensed for the treatment of allergic asthma. The safety profile of omalizumab is well known, and indeed this medication has been used for food allergy, although there is limited trial evidence to support its use and it is not approved by the Food and Drug Administration for this use. The Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen Oral Immunotherapy in Food Allergic Participants (OUtMATCH) trial was designed as a multistage clinical trial to evaluate the safety and efficacy of omalizumab in persons with multiple food allergies.[6]

The OUtMATCH trial has three stages, and Wood et al. now report in the *Journal* the results of the first stage of the trial.[7] The first stage was designed to evaluate the efficacy of omalizumab monotherapy in patients with peanut allergy and allergies to at least two other foods in the prespecified list (cashew, milk, egg, walnut, wheat, and hazelnut). Participants underwent food challenges at baseline and were randomly assigned, in a 2:1 ratio, to receive omalizumab or placebo every 2 to 4 weeks for 16 to 20 weeks, followed by repetition of the food challenges to evaluate the changes in the thresholds of reaction to the allergenic foods. In addition, the first 60 participants who had completed the first stage of the trial continued to a 24-week open-label extension to evaluate the durability of response. The participants were required to avoid their food allergens throughout the trial. The Covid-19 pandemic introduced challenges to conducting the trial, including a reduction in the number of participants; 180 participants were recruited instead of the original plan of 225. The primary end point was consumption of a single dose of at least 600 mg of peanut protein without dose-limiting symptoms at the completion of the first stage of the trial.

Among the 177 participants who were children or adolescents, a significantly greater percentage in the treatment group than in the placebo group (67% vs. 7%) met the primary end-point criterion. Although an increase in the reaction threshold was shown for each of the other foods, the percentage of participants who could successfully consume three of the foods at a cumulative dose of 1044 mg was only 47% in the treatment group. When longer treatment (40 to 44 weeks) was assessed in the open-label extension, the reaction threshold for peanut remained the same as that at the end of the 16-to-20-week period (in 45% of the participants) or increased (in 34%). However, 21% of the participants had a decreased reaction threshold at the end of the extension period. These findings arouse concern about the durability of treatment response. With regard to quality-of-life assessments, no changes from baseline were seen in either caregiver or participant scores at the end of the first stage of the trial.

This trial showed that omalizumab monotherapy was safe and effective in increasing the reaction threshold for peanut and other foods in challenges performed in the hospital setting, but what does this mean for persons with multiple food allergies? In the absence of a curative treatment for food allergy, allergen avoidance has been the cornerstone of the management of food allergy. As a result, quality of life is compromised because of lifestyle restrictions and the constant fear of reactions associated with accidental exposure. Oral immunotherapy for peanut allergy has been shown to be effective in increasing the reaction threshold, but such treatment was associated with more allergic and anaphylactic reactions when compared with the standard recommendation of avoidance.[4] Furthermore, immunotherapy has not been shown to improve the quality of life of patients with peanut allergy.

In clinical trials assessing new therapies for food allergy, investigators have primarily selected reaction thresholds as the primary outcome. In real life, people want treatments that will decrease the risk of accidental allergic reactions, lift the burden on their daily lives, simplify their dietary restrictions, and improve their quality of life. What people want from the treatment will vary according to the severity of the food allergy and other patient-specific quality-of-life preferences. Persons who opt to receive omalizumab must be informed that the possible protection will most likely disappear after omalizumab treatment is stopped. Will those with a history of mild reactions opt for injections on a regular basis over the traditional avoidance approach? Will the use of omalizumab as an adjunct to oral immunotherapy improve the safety profile of oral immunotherapy? For patients who have multiple food allergies and have unacceptable side effects with oral immunotherapy, omalizumab monotherapy could be a useful treatment. Data regarding the possible benefits of omalizumab with respect to important patient-centered outcomes and quality of life are needed before we can make recommendations for patients in clinical practice. Will the use of omalizumab, either as monotherapy or as an adjunct to immunotherapy, really "outmatch" other treatment options for patients with multiple food allergies? The next two stages of the OUtMATCH trial may provide answers to some of the remaining questions.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

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Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Patients with type 2 diabetes and chronic kidney disease are at high risk for kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.

METHODS

We randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.

RESULTS

Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P=0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m^2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P=0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P=0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).

CONCLUSIONS

Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease. (Funded by Novo Nordisk; FLOW ClinicalTrials.gov number, NCT03819153.)

From the University of New South Wales, Sydney (V.P.); the Division of Nephrology, University of Washington School of Medicine, Seattle, and Providence Medical Research Center, Providence Inland Northwest Health, Spokane — both in Washington (K.R.T.); Steno Diabetes Center Copenhagen, Herlev (P.R.), the Department of Clinical Medicine, University of Copenhagen, Copenhagen (P.R.), and Novo Nordisk, Søborg (F.M.M.B., T.I., H.B.-T., N.L.L.) — all in Denmark; Stanford Center for Clinical Research, Department of Medicine, Stanford School of Medicine, Palo Alto, CA (K.W.M.); KfH Kidney Center, Munich, and University Hospital, Friedrich-Alexander University, Erlangen — both in Germany (J.F.E.M.); the Department of Medicine, American Heart Association Comprehensive Hypertension Center, University of Chicago Medicine, Chicago (G.B.); and AdventHealth Translational Research Institute, Orlando, FL (R.P.). Dr. Perkovic can be contacted at vlado.perkovic@unsw.edu.au or at the Chancellery, University of New South Wales, Sydney, NSW 2052, Australia.

*The FLOW Trial Committees and Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide, CKD, and Type 2 Diabetes

A PLAIN LANGUAGE SUMMARY

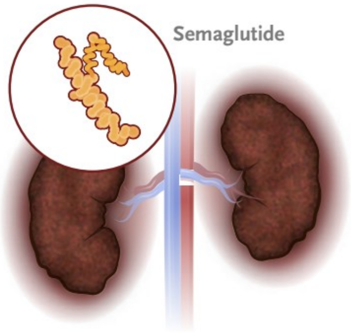
Based on the NEJM publication: Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes by V. Perkovic et al. (published May 24, 2024)

In this trial, researchers assessed whether the glucagon-like peptide 1 (GLP-1) receptor agonist semaglutide was effective in preventing progression of kidney disease in patients with type 2 diabetes and chronic kidney disease (CKD).

Type 2 diabetes is a frequent cause of chronic kidney disease, which can lead to kidney failure, cardiovascular events, and death.

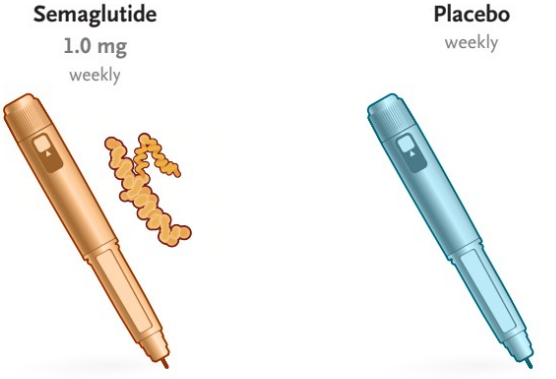
WHY WAS THE TRIAL DONE?

Semaglutide has been shown to improve glycemic control, lead to weight loss, and reduce cardiovascular events in patients with type 2 diabetes. Its effect on kidney outcomes in patients who also have chronic kidney disease is incompletely understood.



HOW WAS THE TRIAL CONDUCTED?

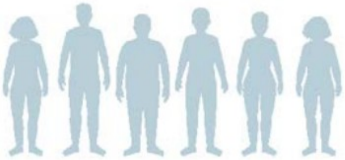
3533 participants with type 2 diabetes and chronic kidney disease were randomly assigned to receive weekly subcutaneous semaglutide (1.0 mg) or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (initiation of dialysis, kidney transplantation, or an estimated glomerular filtration rate [eGFR] of <15 ml per minute per 1.73 m^2), at least a 50% reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes.



1767 Participants

1766 Participants

PARTICIPANTS



WHO	3533 adults Mean age, 67 years Men: 70%; Women: 30%
CLINICAL STATUS	High-risk chronic kidney disease Type 2 diabetes

TRIAL DESIGN

- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 387 SITES IN 28 COUNTRIES

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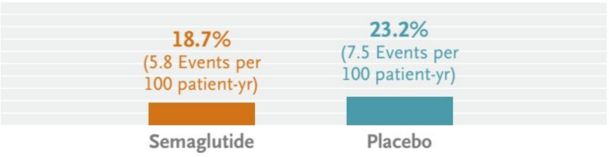
RESULTS

The trial was stopped early at a median follow-up of 3.4 years after an interim analysis showed efficacy. The semaglutide group had fewer primary-outcome events than the placebo group, equivalent to a 24% lower risk with semaglutide.

Major Kidney Disease Events

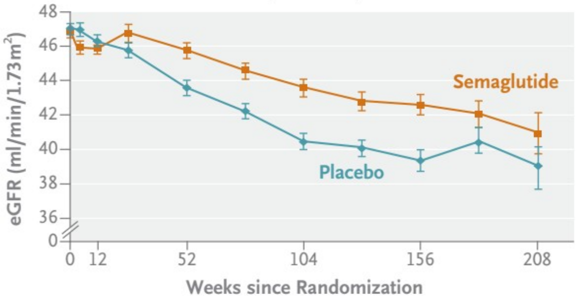
Hazard ratio, 0.76 (95% CI, 0.66–0.88); P=0.0003



Kidney function declined more slowly in the semaglutide group than in the placebo group.

Decline in Kidney Function

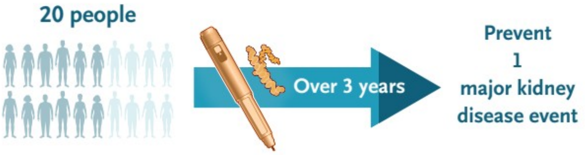
Difference in mean annual decline, 1.16 ml/min/1.73 m^2
95% CI, 0.86–1.47; P<0.001



Serious adverse events were less common in the semaglutide group than in the placebo group.

KIDNEY OUTCOMES

Twenty people would need to be treated with semaglutide over a 3-year period to prevent one major kidney disease event.



LIMITATIONS AND REMAINING QUESTIONS

- Sodium–glucose cotransporter 2 inhibitors and nonsteroidal mineralocorticoid-receptor antagonists were not yet approved for kidney protection when the trial began. Since few participants were receiving those drugs at baseline, the ability of the trial to assess the effects of combination therapy was limited.
- Kidney disease disproportionately affects Black and Indigenous people, who were underrepresented in this trial.
- The effects on kidney function may not be generalizable to other populations, such as persons at lower risk.

CONCLUSIONS

In adults with type 2 diabetes and chronic kidney disease, semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03819153

Trial funding: Novo Nordisk

Full citation: Perkovic V, Tuttle KR, Rossing P, et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. N Engl J Med 2024;391:109-21. DOI: 10.1056/NEJMoa2403347

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EDITORIAL

Diabetic Kidney Disease — Semaglutide Flows into the Mainstream

William G. Herrington, M.D., and Richard Haynes, D.M.

Chronic kidney disease is common and is associated with an increased risk of cardiovascular disease and progression to kidney failure. It has many causes, of which diabetes is the single most common.[1] For many years, renin–angiotensin system (RAS) inhibition was the only treatment that had been proved to slow progression. Since 2019, however, large, randomized trials have shown the benefit of new treatments. Sodium–glucose cotransporter 2 (SGLT2) inhibitors slow the progression of chronic kidney disease and reduce cardiovascular risk, irrespective of the underlying cause of chronic kidney disease,[2] and the nonsteroidal mineralocorticoid-receptor antagonist finerenone has had similar effects among patients with type 2 diabetes and chronic kidney disease with albuminuria.[3] Nevertheless, many patients with chronic kidney disease remain at risk for worsening kidney function and premature cardiovascular disease.

Glucagon-like peptide 1 (GLP-1) receptor agonists are recommended for improvement of glycemic control in patients with type 2 diabetes and chronic kidney disease[1,4] because these medications are known to reduce the risk of cardiovascular disease, with consistent effects among patients with an estimated glomerular filtration rate (eGFR) of 60 milliliters per minute per 1.73 m^2 of body-surface area or higher and those with an eGFR below that threshold.[5] However, patients with more advanced chronic kidney disease have been underrepresented in previous trials, and the effect that GLP-1 receptor agonists have on albuminuria has not yet been shown to translate into a reduced risk of kidney failure.[5]

The Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, the results of which are reported in this issue of the *Journal*,[6] provides evidence that the GLP-1 receptor agonist semaglutide, alongside other therapies, should emerge as a first-line treatment for patients with type 2 diabetes with chronic kidney disease and albuminuria. In the trial, 3533 participants (mean body-mass index [the weight in kilograms divided by the square of the height in meters], 32) who had chronic kidney disease and were at risk for disease progression were randomly assigned to receive subcutaneous semaglutide or matching placebo. The prespecified primary outcome was a composite of kidney failure, a sustained decrease of at least 50% in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Over a median follow-up of 3.4 years, semaglutide led to a 24% lower risk (95% confidence interval [CI], 12 to 34) of a primary-outcome event than placebo, with consistent effects across the individual components of the outcome and across prespecified subgroups. Semaglutide reduced the risk of major cardiovascular events by 18% (95% CI, 2 to 32) and the risk of death from cardiovascular causes by 29% (95% CI, 11 to 44; 123 vs. 169 deaths). Semaglutide had no effect on death from kidney-related or other noncardiovascular causes combined (104 vs. 110 deaths), so the risk of death from any cause was 20% lower (95% CI, 5 to 33) with semaglutide than with placebo. Such clear benefits necessitated early termination of the trial.

The FLOW trial was not designed to show an effect on kidney failure alone; nevertheless, the effects of semaglutide on the eGFR suggest renoprotection. The eGFR slope data are particularly intriguing, since they represent a pattern that is potentially distinct from that observed with RAS inhibitors, SGLT2 inhibitors, and finerenone. These interventions all cause a clear acute "dip" in eGFR on initiation, followed by a slowing of the decline in the eGFR over the long term.[7,8] In the FLOW trial, semaglutide did not result in a difference in eGFR from placebo at 12 weeks, and then the eGFR slopes diverged. Overall, the between-group difference of 1.16 ml per minute per 1.73 m^2 per year in the creatinine-based eGFR slope represents a reduction of approximately one third in the annual rate of eGFR decline (i.e., total slope). The reduction in the urinary albumin-to-creatinine ratio caused by semaglutide in the FLOW trial suggests that the drug does target glomerular dysfunction; however, its effects on weight (4.1 kg greater weight loss in the semaglutide group than in the placebo group) and glycated hemoglobin levels (0.81 percentage points greater decrease in the semaglutide group) in this trial seem unlikely to be the sole explanation for its salutary effects on the kidney, and its mechanisms of renoprotection are the subject of an ongoing trial (ClinicalTrials.gov number, NCT04865770).

The benefits of semaglutide went beyond those conferred by use of a RAS inhibitor (95% of FLOW participants were already taking such treatment). At baseline, the percentage of patients taking SGLT2 inhibitors was 16%, with very likely no participants taking finerenone. Given that we predict different mechanisms of renoprotection from semaglutide, it is reasonable to postulate that GLP-1 receptor agonists will confer additional benefits beyond those of other therapies. Now the key question is how best to implement semaglutide treatment alongside SGLT2 inhibitors and finerenone, not whether to do so.

GLP-1 receptor agonists do cause nausea and other gastrointestinal disturbances,[9] yet the proportion of patients who discontinued semaglutide at the dose studied in the FLOW trial (1.0 mg per week initiated with an 8-week dose escalation) was similar to the proportion who discontinued placebo. The percentage of patients who had "acute kidney failure" or severe hypoglycemia as an adverse event did not differ between the groups. Complementing these FLOW data are cardiovascular and potential renal benefits reported in the recent Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, which involved a population with preexisting atherosclerotic cardiovascular disease without diabetes (in which the dose of 2.4 mg per week was tested).[9,10] Together, these data should be a stimulus for embarking on large renoprotection trials of GLP-1 receptor agonists for patients without diabetes (including patients with causes of chronic kidney disease that made them ineligible for the FLOW trial), as well as for persons with diabetes and minimal or modest albuminuria.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

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Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis

R. Loomba, M.L. Hartman, E.J. Lawitz, R. Vuppalanchi, J. Boursier, E. Bugianesi, M. Yoneda, C. Behling, O.W. Cummings, Y. Tang, B. Brouwers, D.A. Robins, A. Nikooie, M.C. Bunck, A. Haupt, and A.J. Sanyal, for the SYNERGY-NASH Investigators*

ABSTRACT

BACKGROUND

Metabolic dysfunction–associated steatohepatitis (MASH) is a progressive liver disease associated with liver-related complications and death. The efficacy and safety of tirzepatide, an agonist of the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, in patients with MASH and moderate or severe fibrosis is unclear.

METHODS

We conducted a phase 2, dose-finding, multicenter, double-blind, randomized, placebo-controlled trial involving participants with biopsy-confirmed MASH and stage F2 or F3 (moderate or severe) fibrosis. Participants were randomly assigned to receive once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at 52 weeks. A key secondary end point was an improvement (decrease) of at least one fibrosis stage without worsening of MASH.

RESULTS

Among 190 participants who had undergone randomization, 157 had liver-biopsy results at week 52 that could be evaluated, with missing values imputed under the assumption that they would follow the pattern of results in the placebo group. The percentage of participants who met the criteria for resolution of MASH without worsening of fibrosis was 10% in the placebo group, 44% in the 5-mg tirzepatide group (difference vs. placebo, 34 percentage points; 95% confidence interval [CI], 17 to 50), 56% in the 10-mg tirzepatide group (difference, 46 percentage points; 95% CI, 29 to 62), and 62% in the 15-mg tirzepatide group (difference, 53 percentage points; 95% CI, 37 to 69) ($P<0.001$ for all three comparisons). The percentage of participants who had an improvement of at least one fibrosis stage without worsening of MASH was 30% in the placebo group, 55% in the 5-mg tirzepatide group (difference vs. placebo, 25 percentage points; 95% CI, 5 to 46), 51% in the 10-mg tirzepatide group (difference, 22 percentage points; 95% CI, 1 to 42), and 51% in the 15-mg tirzepatide group (difference, 21 percentage points; 95% CI, 1 to 42). The most common adverse events in the tirzepatide groups were gastrointestinal events, and most were mild or moderate in severity.

CONCLUSIONS

In this phase 2 trial involving participants with MASH and moderate or severe fibrosis, treatment with tirzepatide for 52 weeks was more effective than placebo with respect to resolution of MASH without worsening of fibrosis. Larger and longer trials are needed to further assess the efficacy and safety of tirzepatide for the treatment of MASH. (Funded by Eli Lilly; SYNERGY-NASH ClinicalTrials.gov number, NCT04166773.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Loomba can be contacted at roloomba@health.ucsd.edu or at the Metabolic Dysfunction–Associated Steatotic Liver Disease Research Center, Division of Gastroenterology and Hepatology, Department of Medicine, University of California at San Diego, La Jolla, CA 92037.

*A complete list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Loomba and Hartman contributed equally to this article.

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The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for MASH with Liver Fibrosis

A PLAIN LANGUAGE SUMMARY

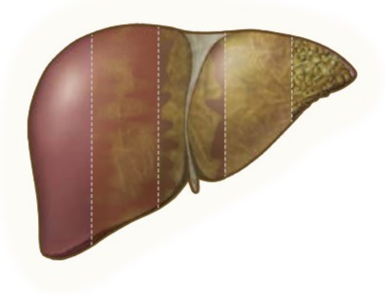
Based on the NEJM publication: Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis by R. Loomba et al. (published June 8, 2024)

In this trial, researchers assessed the efficacy and safety of once-weekly tirzepatide in persons with metabolic dysfunction–associated steatohepatitis (MASH) and moderate or severe fibrosis.

MASH, formerly known as NASH (nonalcoholic steatohepatitis), is a progressive liver disease characterized by excess fat in the liver, hepatic inflammation, and hepatocyte injury, with or without fibrosis.

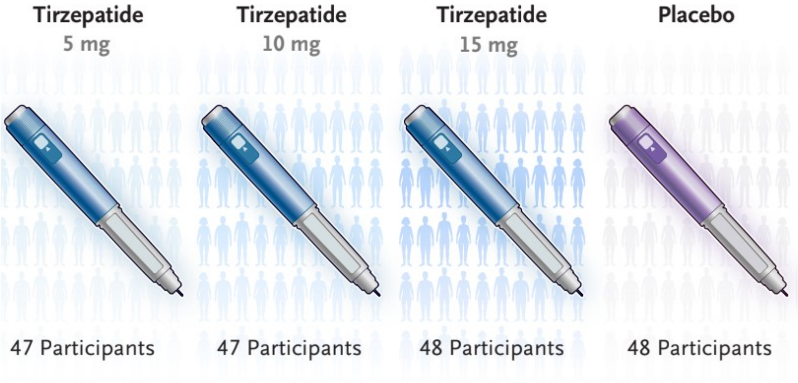
WHY WAS THE TRIAL DONE?

MASH is associated with liver-related complications and death. Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist, has been shown to reduce liver fat and improve biomarkers of MASH and fibrosis in persons with type 2 diabetes. The efficacy and safety of tirzepatide in persons with MASH and moderate or severe fibrosis are unclear.

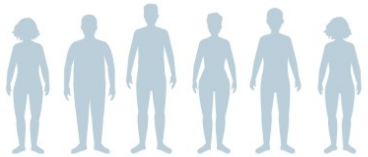


HOW WAS THE TRIAL CONDUCTED?

190 adults with a body-mass index (BMI) between 27 and 50, histologically confirmed MASH, and moderate or severe fibrosis received once-weekly subcutaneous tirzepatide at one of three doses (5 mg, 10 mg, or 15 mg) or placebo for 52 weeks. The primary end point was resolution of MASH without worsening of fibrosis at week 52.



PARTICIPANTS



WHO	**190 participants** **18 to 80 years of age** **Women: 57%; Men: 43%**
CLINICAL STATUS	**Biopsy-confirmed MASH** **Stage 2 or 3 fibrosis** **BMI, 27 to 50** **With or without type 2 diabetes mellitus**

TRIAL DESIGN

- PHASE 2
- MULTICENTER
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 10 COUNTRIES

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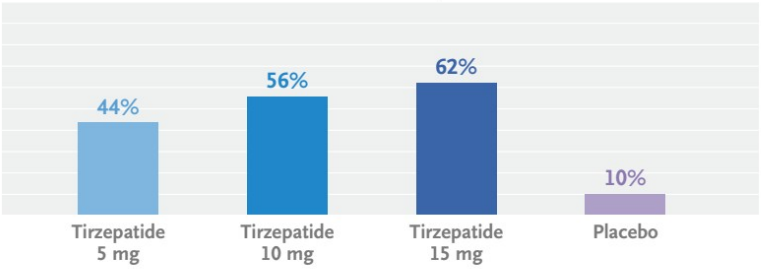
RESULTS

The percentage of participants who had resolution of MASH without worsening of fibrosis was significantly higher in all three tirzepatide groups than in the placebo group.

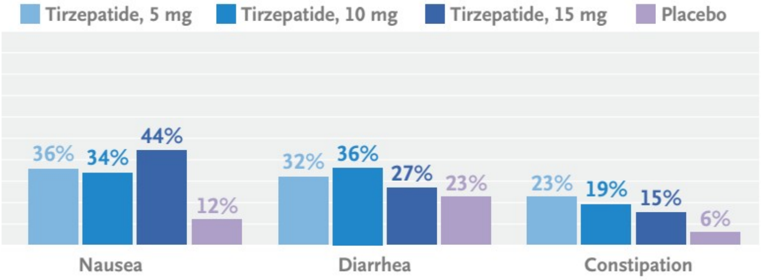
Resolution of MASH and No Worsening of Fibrosis

P<0.001 for all three comparisons



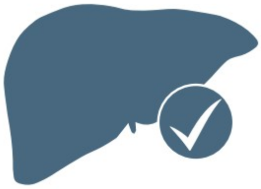
Gastrointestinal events were the most common adverse events with tirzepatide and were mostly mild or moderate in severity.

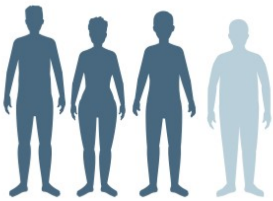
Adverse Events



FIBROSIS STAGE

The percentage of participants who had an improvement (decrease) of at least one fibrosis stage without worsening of MASH (a key secondary end point) also favored the tirzepatide groups.





LIMITATIONS AND REMAINING QUESTIONS

- The small sample size did not provide adequate statistical power to evaluate the effect of tirzepatide on fibrosis.
- The trial was too short to assess the effect of tirzepatide on major adverse liver outcomes.
- Persons with MASH that had progressed to cirrhosis were not included in the trial.

CONCLUSIONS

In participants with MASH and moderate or severe fibrosis, once-weekly tirzepatide at a dose of 5 mg, 10 mg, or 15 mg was more effective than placebo for resolution of MASH without worsening of fibrosis.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04166773

Trial funding: Eli Lilly

Full citation: Loomba R, Hartman ML, Lawitz EJ, et al. Tirzepatide for metabolic dysfunction–associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391:299-310. DOI: 10.1056/NEJMoa2401943

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EDITORIAL

Dual Agonists for Management of Metabolic Dysfunction–Associated Steatohepatitis

Fasiha Kanwal, M.D., M.S.H.S.

Metabolic dysfunction–associated steatohepatitis (MASH) is the most common liver disease worldwide, and its prevalence is increasing rapidly.[1] Yet, effective treatments for MASH remain scarce. Obesity plays a central role in MASH. Glucagon-like peptide-1 (GLP-1) receptor agonists are emerging as the most promising antiobesity treatments[2] and could serve as an option for patients with MASH. Few studies have examined the efficacy of GLP-1 receptor agonists in MASH. In a phase 2 trial, treatment with semaglutide — a GLP-1 receptor agonist — led to resolution of steatohepatitis in 40 to 59% of patients but fell short of showing a significant reduction in liver fibrosis.[3] In patients with MASH, a reduction in fibrosis is arguably a more important surrogate end point than resolution of steatohepatitis. Treatment with semaglutide also did not improve histologic outcomes in patients with MASH that had progressed to cirrhosis.[4]

The metabolic effects of GLP-1 receptor agonists can potentially be enhanced by combining their actions with those of other incretin hormones or molecules affecting alternative yet complementary pathways. In this issue of the *Journal*, Loomba et al.[5] and Sanyal et al.[6] report the results of two phase 2 trials of these enhanced GLP-1 receptor agonist–based treatments. Tirzepatide consists of a GLP-1 receptor agonist and a glucose-dependent insulinotropic polypeptide receptor agonist, which have synergistic effects on appetite, food intake, and metabolic function.[7,8] Similarly, survodutide, a dual agonist of GLP-1 receptor and glucagon receptor,[9] provides benefit by promoting fat oxidation and reducing lipid synthesis in the hepatocytes through its direct action on glucagon receptors in the liver.[10]

In the trial by Loomba et al., tirzepatide was evaluated in adults with MASH and stage 2 or 3 fibrosis. The percentage of those who had resolution of MASH without worsening of fibrosis at 52 weeks (the primary end point) was 44%, 56%, and 62% with 5-mg, 10-mg, and 15-mg once-weekly doses of tirzepatide, respectively, as compared with 10% of the participants who received placebo. In total, approximately 50% of the participants in the tirzepatide groups had an improvement (decrease) in liver fibrosis of at least one stage without worsening of MASH as compared with 30% in the placebo group. Participants who received tirzepatide had a mean reduction in body weight of up to 16% (with the 15-mg dose). The safety profile of tirzepatide was consistent with previous findings in persons with obesity[11] and type 2 diabetes.[12] The most common adverse events were gastrointestinal events, most of which were mild or moderate in severity. Less than 5% of the adverse events that were reported during the trial led to discontinuation of tirzepatide or placebo. Nearly 87% of the participants completed the trial.

The trial by Sanyal et al. examined the use of survodutide in adults with MASH and stage 1, 2, or 3 fibrosis.[6] Histologic improvement (reduction) in MASH without worsening of fibrosis at 48 weeks (the primary end point) occurred in 47%, 62%, and 43% of the participants who received 2.4-mg, 4.8-mg, and 6.0-mg doses of survodutide once weekly, respectively, as compared with 14% of those who received placebo. Improvement (reduction) in fibrosis of at least one stage with no worsening of MASH was seen in 32% of the participants in the survodutide 6.0-mg group as compared with 18% of those in the placebo group. Participants in the survodutide groups lost 10 to 13% of their body weight. The percentage of participants who discontinued survodutide was high. One in five participants who were receiving survodutide dropped out during the rapid-dose-escalation phase because of adverse events. Among the participants assigned to the survodutide 6.0-mg group, only 70% underwent dose escalation to this threshold. Most of the adverse events that occurred were gastrointestinal events, but fatigue, increases in pancreatic enzyme levels, and tachycardia occurred more frequently with survodutide than with placebo.

There is an urgent need for safe and effective treatments for MASH. By showing the effectiveness of dual agonists in patients with MASH, these trials represent a substantial step forward. Together, they also highlight the potential for pharmacologic treatments to lead to an improvement of at least 30% in histologic outcomes, including fibrosis — data that are encouraging for patients and their clinicians alike.

Despite their importance, both trials were small, which could explain the lack of a clear dose response. Their applicability to the wider population is also debatable. In the trial by Sanyal et al., 20% of the participants in the active-treatment groups discontinued treatment owing to an adverse event, and those who had minimal unacceptable side effects after receiving higher doses may represent a subgroup of the general population. The burden of chronic conditions is disproportionately felt within historically marginalized communities, and the fact that the trials included few members of minoritized groups, especially Blacks, was discouraging. Both trials were of short duration. Results of withdrawal trials of antiobesity medications have consistently shown substantial weight regain with cessation of therapy.[13] MASH is a chronic condition and will probably necessitate continued treatment to maintain and augment histologic gains, although questions remain regarding when to stop treatments and in whom they should be stopped. Such long-term treatment could also be associated with substantial costs and barriers to access that may widen health inequalities unless safeguards are in place. The results of the two trials also left open questions about the effectiveness of the treatments in patients with cirrhosis.

Overall, these data are encouraging. Clinicians providing care for patients with MASH will probably have an increasing number of options in their armamentarium. With a growing menu of effective treatments, harms and unacceptable side effects will be important considerations in making treatment decisions.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, the Veterans Affairs Health Systems Research Center for Innovations in Quality, Effectiveness, and Safety, and the Michael E. DeBakey Veterans Affairs Medical Center — all in Houston.

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ORIGINAL ARTICLE

Cognitive Motor Dissociation in Disorders of Consciousness

Y.G. Bodien, J. Allanson, P. Cardone, A. Bonhomme, J. Carmona, C. Chatelle, S. Chennu, M. Conte, S. Dehaene, P. Finoia, G. Heinonen, J.E. Hersh, E. Kamau, P.K. Lawrence, V.C. Lupson, A. Meydan, B. Rohaut, W.R. Sanders, J.D. Sitt, A. Soddu, M. Valente, A. Velazquez, H.U. Voss, A. Vrosgou, J. Claassen, B.L. Edlow, J.J. Fins, O. Gosseries, S. Laureys, D. Menon, L. Naccache, A.M. Owen, J. Pickard, E.A. Stamatakis, A. Thibaut, J.D. Victor, J.T. Giacino, E. Bagiella, and N.D. Schiff

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ABSTRACT

BACKGROUND

Patients with brain injury who are unresponsive to commands may perform cognitive tasks that are detected on functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). This phenomenon, known as cognitive motor dissociation, has not been systematically studied in a large cohort of persons with disorders of consciousness.

METHODS

In this prospective cohort study conducted at six international centers, we collected clinical, behavioral, and task-based fMRI and EEG data from a convenience sample of 353 adults with disorders of consciousness. We assessed the response to commands on task-based fMRI or EEG in participants without an observable response to verbal commands (i.e., those with a behavioral diagnosis of coma, vegetative state, or minimally conscious state–minus) and in participants with an observable response to verbal commands. The presence or absence of an observable response to commands was assessed with the use of the Coma Recovery Scale–Revised (CRS-R).

RESULTS

Data from fMRI only or EEG only were available for 65% of the participants, and data from both fMRI and EEG were available for 35%. The median age of the participants was 37.9 years, the median time between brain injury and assessment with the CRS-R was 7.9 months (25% of the participants were assessed with the CRS-R within 28 days after injury), and brain trauma was an etiologic factor in 50%. We detected cognitive motor dissociation in 60 of the 241 participants (25%) without an observable response to commands, of whom 11 had been assessed with the use of fMRI only, 13 with the use of EEG only, and 36 with the use of both techniques. Cognitive motor dissociation was associated with younger age, longer time since injury, and brain trauma as an etiologic factor. In contrast, responses on task-based fMRI or EEG occurred in 43 of 112 participants (38%) with an observable response to verbal commands.

CONCLUSIONS

Approximately one in four participants without an observable response to commands performed a cognitive task on fMRI or EEG as compared with one in three participants with an observable response to commands. (Funded by the James S. McDonnell Foundation and others.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 3, 2024 VOL. 391 NO. 13

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

ABSTRACT

BACKGROUND

There are gaps in uptake of, adherence to, and persistence in the use of preexposure prophylaxis for human immunodeficiency virus (HIV) prevention among cisgender women.

METHODS

We conducted a phase 3, double-blind, randomized, controlled trial involving adolescent girls and young women in South Africa and Uganda. Participants were assigned in a 2:2:1 ratio to receive subcutaneous lenacapavir every 26 weeks, daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF; active control); all participants also received the alternate subcutaneous or oral placebo. We assessed the efficacy of lenacapavir and F/TAF by comparing the incidence of HIV infection with the estimated background incidence in the screened population and evaluated relative efficacy as compared with F/TDF.

RESULTS

Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed: 0 infections among 2134 participants in the lenacapavir group (0 per 100 person-years; 95% confidence interval [CI], 0.00 to 0.19), 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74). Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19). HIV incidence with lenacapavir was significantly lower than background HIV incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001) and than HIV incidence with F/TDF (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001). HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P=0.21), and no evidence of a meaningful difference in HIV incidence was observed between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14). Adherence to F/TAF and F/TDF was low. No safety concerns were found. Injection-site reactions were more common in the lenacapavir group (68.8%) than in the placebo injection group (F/TAF and F/TDF combined) (34.9%); 4 participants in the lenacapavir group (0.2%) discontinued the trial regimen owing to injection-site reactions.

CONCLUSIONS

No participants receiving twice-yearly lenacapavir acquired HIV infection. HIV incidence with lenacapavir was significantly lower than background HIV incidence and HIV incidence with F/TDF. (Funded by Gilead Sciences; PURPOSE 1 ClinicalTrials.gov number, NCT04994509.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Das can be contacted at moupali.das@gilead.com or at Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404.

*The members of the PURPOSE 1 Study Team are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on July 24, 2024, at NEJM.org.

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DOI: 10.1056/NEJMoa2407001

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The NEW ENGLAND JOURNAL of MEDICINE

Twice-Yearly Lenacapavir for HIV Prevention

A PLAIN LANGUAGE SUMMARY

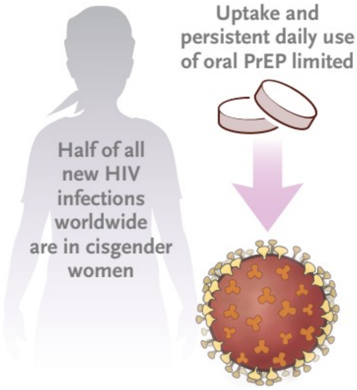
Based on the NEJM publication: Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women
by L.-G. Bekker et al. (published July 24, 2024)

In this trial, researchers evaluated the efficacy and safety of twice-yearly subcutaneous lenacapavir or daily oral emtricitabine–tenofovir alafenamide (F/TAF) for human immunodeficiency virus (HIV) prevention in cisgender adolescent girls and young women.

Lenacapavir is a first-in-class, multistage HIV-1 capsid inhibitor with a long half-life, allowing administration by subcutaneous injection twice a year.

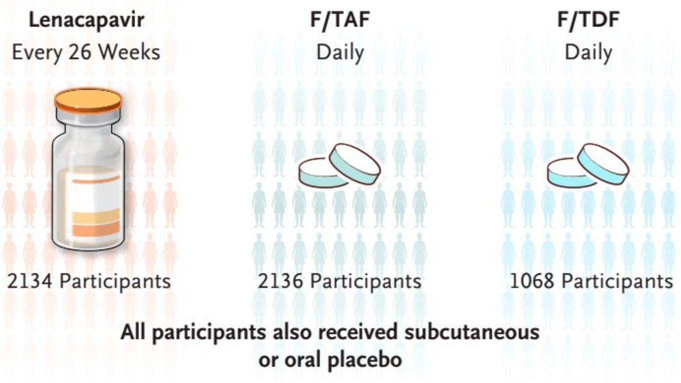
WHY WAS THE TRIAL DONE?

Cisgender women account for approximately half the 1.3 million new HIV infections that occur worldwide each year. Daily oral preexposure prophylaxis (PrEP) is effective if taken as directed but is suboptimal, particularly in certain populations with disproportionate HIV incidence. New preventive options are needed.

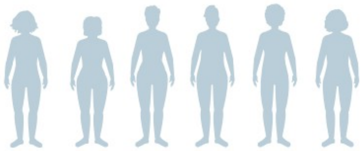

Uptake and persistent daily use of oral PrEP limited
Half of all new HIV infections worldwide are in cisgender women

HOW WAS THE TRIAL CONDUCTED?

Adolescent girls and women who were HIV-negative at baseline were assigned to receive subcutaneous lenacapavir every 26 weeks, daily oral F/TAF, or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF; active control) for 104 weeks. All participants also received the alternate subcutaneous or oral placebo. The primary objective was to determine the efficacy of lenacapavir and F/TAF by comparing the incidence of HIV infection among participants with the estimated background incidence in a cross-sectional screened incidence cohort.


Lenacapavir
Every 26 Weeks
2134 Participants
F/TAF
Daily
2136 Participants
F/TDF
Daily
1068 Participants
All participants also received subcutaneous or oral placebo

PARTICIPANTS



WHO	**5338 adolescent girls and young women in South Africa and Uganda** **Median age, 21 years (range, 16 to 26)**
CLINICAL STATUS	**Sexually active with male partners** **Not using PrEP** **Unknown HIV status and no HIV testing within the previous 3 months (screening population)**

TRIAL DESIGN

- PHASE 3
- MULTICENTER
- DOUBLE-BLIND
- RANDOMIZED
- ACTIVE-CONTROLLED
- LOCATIONS: 25 IN SOUTH AFRICA AND 3 IN UGANDA

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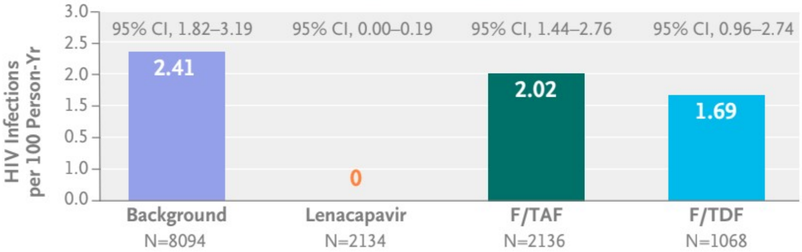
RESULTS

Twice-yearly lenacapavir reduced HIV incidence by 100% as compared with background HIV incidence and by 100% as compared with daily oral F/TDF. No adolescent girls or young women who received lenacapavir acquired HIV infection.

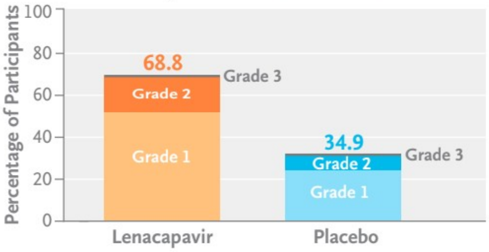
HIV incidence with F/TAF did not differ significantly from background HIV incidence, and there was no meaningful difference in HIV incidence between F/TAF and F/TDF.

Incident HIV Infections



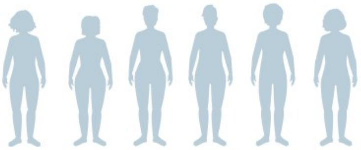
Injection-site reactions were the most common adverse event and were more common in the lenacapavir group than in the other groups.

Injection-Site Reactions



ADHERENCE

SUN
MON
TUE
WED
THU
FRI
SAT



Adherence to F/TAF and F/TDF was assessed on the basis of tenofovir diphosphate levels and was found to be poor. Efficacy was correlated with adherence.

LIMITATIONS AND REMAINING QUESTIONS

- Further monitoring for breakthrough HIV infection and evidence of delayed HIV seroconversion with lenacapavir use is warranted; the open-label extension phase of this trial may provide further insight.
- There was no longitudinal follow-up for the background incidence of HIV infection, which was a cross-sectional estimate derived during the screening period.

CONCLUSIONS

In a randomized, controlled trial involving cisgender adolescent girls and young women in South Africa and Uganda, twice-yearly subcutaneous lenacapavir was superior to daily oral emtricitabine–tenofovir disoproxil fumarate in preventing HIV infection.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04994509

Trial funding: Gilead Sciences

Full citation: Bekker L-G, Das M, Abdool Karim Q, et al. Twice-yearly lenacapavir or daily F/TAF for HIV prevention in cisgender women. N Engl J Med 2024;391:1179-92. DOI: 10.1056/NEJMoa2407001

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EDITORIAL

The Real PURPOSE of PrEP — Effectiveness, Not Efficacy

Rochelle P. Walensky, M.D., M.P.H., and Lindsey R. Baden, M.D.

Given the 40 years of research and the wealth of successful tools that have been developed to prevent, diagnose, treat, and suppress human immunodeficiency virus (HIV) infection, how is it possible that in 2024 the incidence of HIV type 1 (HIV-1) infection is more than 3.5 per 100 person-years among young women in southern Africa?[1] The efficacy of preexposure prophylaxis (PrEP) to prevent HIV infection was first shown in 2010 in the landmark Preexposure Prophylaxis Initiative (iPrEx) trial of emtricitabine–tenofovir disoproxil fumarate (F/TDF), largely in men who have sex with men (MSM).[2] In July 2012, the time of Food and Drug Administration approval of F/TDF for HIV-1 PrEP in MSM, heated discussion ensued about whether these findings might be extrapolated to support PrEP use in other high-risk populations, such as cisgender women.

Bekker et al.[1] now report in the *Journal* the results of a well-done, large, randomized, controlled trial in South Africa and Uganda of PrEP for cisgender women (PURPOSE 1). Participants were assigned in a 2:2:1 ratio to receive twice-yearly subcutaneous lenacapavir (an HIV-1 capsid inhibitor), daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral F/TDF (active control). Given that inclusion of a placebo group was considered to be unethical, screened persons who tested positive for HIV infection underwent further testing to assess the recency of infection; these data were used to estimate the background HIV incidence among all the persons screened.

The background HIV incidence in the screened population sadly mirrored previous estimates, at 2.41 per 100 person-years. Of the 55 incident infections among participants in the three intervention groups, there were none in the lenacapavir group, 39 in the F/TAF group, and 16 in the F/TDF group, with an incidence of 0, 2.02, and 1.69 per 100 person-years, respectively. This efficacy exceeded the predefined stopping criteria, and the trial was stopped early. Meta-analyses have previously shown a dose-responsive PrEP efficacy, depending on adherence.[3] Although it is always challenging to fully understand a postrandomization assessment, because medication adherence and other behaviors may track together, the PURPOSE 1 trial corroborates these gradient findings. Nevertheless, adherence and active drug at the time and site of HIV-1 exposure are probably both important for effective prevention. Findings from the PURPOSE 1 trial underscore the challenges of adherence to a daily oral medication, and the incidence of HIV-1 infection was no different from background incidence when documented adherence was low. With approximately 92% attendance for the twice-yearly lenacapavir injections, the PURPOSE 1 trial exemplifies not only that women can dependably adhere to this administration schedule but also that levels of an HIV-1 capsid inhibitor can remain high enough over a period of 6 months to reliably prevent infection.

The results of the PURPOSE 1 trial will raise scientific questions. For example, how can we address the diagnostic challenges of rare acute HIV-1 infection (as shown in the cabotegravir PrEP studies also now reported in the *Journal*[4])? What are the best tactics to combat the large number of concomitant sexually transmitted infections? What is the potential for emergent viral resistance? How do these data inform potential use for other groups at high risk for HIV infection? And how can we improve contraceptive options for women at high risk for HIV infection. Given the high pregnancy rate among participants in the PURPOSE 1 trial, assessment of the safety of lenacapavir in pregnancy is a priority. Perhaps, however, the most critical question is how — more than a decade after PrEP was first approved in the United States and several years after the promising DISCOVER results among MSM[5] — we have failed women at high risk for HIV infection for so long.

A key challenge to decreasing the incidence of HIV infection is identifying high-risk populations (especially women), engaging them, and providing them easy, low-barrier, and low-cost access to a PrEP regimen that works and to which they can adhere. Because previous PrEP regimens have proven to be highly effective when taken as prescribed, the PURPOSE 1 trial uniquely addresses only the last among these hurdles.

South Africa, the primary country of enrollment in the PURPOSE 1 trial, updated its PrEP guidelines in 2021, endorsing PrEP use for persons at greatest risk for HIV infection, including adolescent girls and young women as well as MSM, among others.[6] Demographic data for South Africa suggest there are approximately 4.5 million adolescent girls and young women between the ages of 16 and 25 years (PURPOSE 1 enrollment criterion), and the Joint United Nations Program on HIV/AIDS estimates an additional 750,000 South Africans among PrEP-eligible key populations.[7] With more than 5.25 million eligible South Africans, as of 2021 a mere 350,000 (<7%) had ever received a PrEP prescription; durable use is probably far lower.

Reported barriers to PrEP use among young persons in the African context include social stigma, fear of side effects, long travel or wait times for appointments, inconvenient clinical operating hours, and drug costs.[8] To bridge the current canyon between PrEP efficacy and effectiveness, future efforts must address these challenges. To start, PrEP drugs proven to work should be financially accessible to the populations in the countries studied. F/TDF is available in South Africa for less than $50 per year. Meanwhile, lenacapavir currently costs approximately $43,000 annually in the United States, according to Red Book Online (Truven Health Analytics), and access to lenacapavir in South Africa is severely limited. But, the results of the PURPOSE 1 trial have now created a moral imperative to make lenacapavir broadly accessible and affordable as PrEP to persons who were enrolled, as well as all those who are similarly eligible and could benefit.[9]

So now we have a PrEP product with high efficacy. That is great news for science but not (yet) great for women. Now, the imperative is to spend time, resources, and political will on access, implementation, and delivery. And that plan must include a mechanism to finance these drugs so that the women who have borne an unacceptably high HIV infection burden and who have volunteered for decades in studies of HIV prevention can reap the PrEP benefits and remain HIV free.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Harvard Kennedy School of Government and Harvard Business School, Cambridge, MA (R.P.W.).

This editorial was published on July 24, 2024, and updated on August 6, 2024, at NEJM.org.

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DOI: 10.1056/NEJMe2408591

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 17, 2024 VOL. 391 NO. 15

Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma

A.F. Herrera, M. LeBlanc, S.M. Castellino, H. Li, S.C. Rutherford, A.M. Evens, K. Davison, A. Punnett, S.K. Parsons, S. Ahmed, C. Casulo, N.L. Bartlett, J.M. Tuscano, M.G. Mei, B.T. Hess, R. Jacobs, H. Saeed, P. Torka, B. Hu, C. Moskowitz, S. Kaur, G. Goyal, C. Forlenza, A. Doan, A. Lamble, P. Kumar, S. Chowdhury, B. Brinker, N. Sharma, A. Singh, K.A. Blum, A.M. Perry, A. Kovach, D. Hodgson, L.S. Constine, L.K. Shields, A. Prica, H. Dillon, R.F. Little, M.A. Shipp, M. Crump, B. Kahl, J.P. Leonard, S.M. Smith, J.Y. Song, K.M. Kelly, and J.W. Friedberg

ABSTRACT

BACKGROUND

Incorporating brentuximab vedotin into the treatment of advanced-stage classic Hodgkin's lymphoma improves outcomes in adult and pediatric patients. However, brentuximab vedotin increases the toxic effects of treatment in adults, more than half of pediatric patients who receive the drug undergo consolidative radiation, and relapse remains a challenge. Programmed death 1 blockade is effective in Hodgkin's lymphoma, including in preliminary studies involving previously untreated patients.

METHODS

We conducted a phase 3, multicenter, open-label, randomized trial involving patients at least 12 years of age with stage III or IV newly diagnosed Hodgkin's lymphoma. Patients were randomly assigned to receive brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine (BV+AVD) or nivolumab with doxorubicin, vinblastine, and dacarbazine (N+AVD). Prespecified patients could receive radiation therapy directed to residual metabolically active lesions. The primary end point was progression-free survival, defined as the time from randomization to the first observation of progressive disease or death from any cause.

RESULTS

Of 994 patients who underwent randomization, 970 were included in the intention-to-treat population for efficacy analyses. At the second planned interim analysis, with a median follow-up of 12.1 months, the threshold for efficacy was crossed, indicating that N+AVD significantly improved progression-free survival as compared with BV+AVD (hazard ratio for disease progression or death, 0.48; 99% confidence interval [CI], 0.27 to 0.87; two-sided $P=0.001$). Owing to the short follow-up time, we repeated the analysis with longer follow-up; with a median follow-up of 2.1 years (range, 0 to 4.2 years), the 2-year progression-free survival was 92% (95% CI, 89 to 94) with N+AVD, as compared with 83% (95% CI, 79 to 86) with BV+AVD (hazard ratio for disease progression or death, 0.45; 95% CI, 0.30 to 0.65). Overall, 7 patients received radiation therapy. Immune-related adverse events were infrequent with nivolumab; brentuximab vedotin was associated with more treatment discontinuation.

CONCLUSIONS

N+AVD resulted in longer progression-free survival than BV+AVD in adolescents and adults with stage III or IV advanced-stage classic Hodgkin's lymphoma and had a better side-effect profile. (Funded by the National Cancer Institute of the National Institutes of Health and others; S1826 ClinicalTrials.gov number, NCT03907488.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Friedberg can be contacted at jonathan_friedberg@urmc.rochester.edu or at the University of Rochester Wilmot Cancer Institute, 601 Elmwood Ave., Box 704, Rochester, NY 14642.

N Engl J Med 2024;391:1379-89.
DOI: 10.1056/NEJMoa2405888

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The NEW ENGLAND JOURNAL of MEDICINE

Nivolumab in Advanced Hodgkin's Lymphoma

A PLAIN LANGUAGE SUMMARY

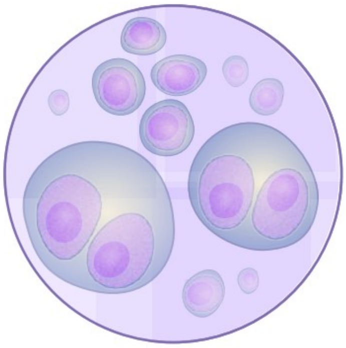
Based on the NEJM publication: Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma
by A.F. Herrera et al. (published October 17, 2024)

In this trial, researchers assessed the efficacy and safety of nivolumab plus chemotherapy with doxorubicin, vinblastine, and dacarbazine (N+AVD), as compared with brentuximab vedotin plus AVD (BV+AVD), in patients with newly diagnosed classic Hodgkin's lymphoma.

Combination chemotherapy has been the standard treatment of **advanced-stage classic Hodgkin's lymphoma** for decades.

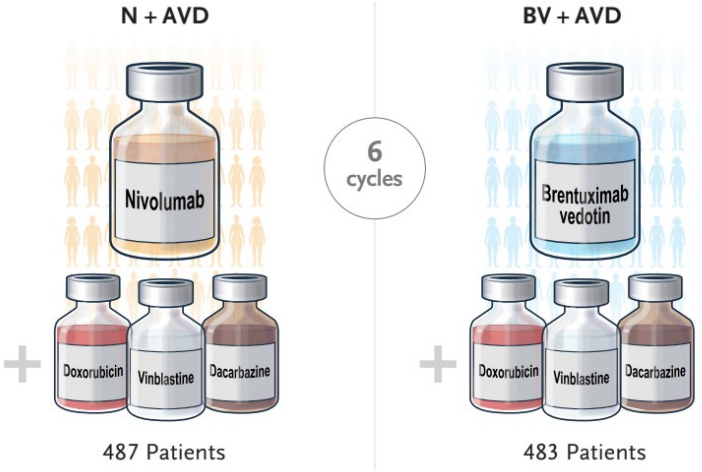
WHY WAS THE TRIAL DONE?

Adding brentuximab vedotin, a CD30-directed antibody drug conjugate, to chemotherapy improves outcomes in advanced-stage classic Hodgkin's lymphoma as compared with standard ABVD chemotherapy (AVD plus bleomycin). However, brentuximab vedotin is associated with increased toxic effects in adults, and relapses remain problematic. How treatment with nivolumab, a programmed death receptor 1 (PD-1) inhibitor, compares with brentuximab vedotin is unknown.

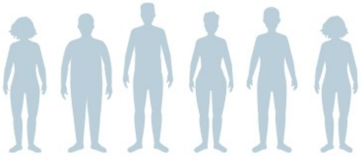


HOW WAS THE TRIAL CONDUCTED?

Patients 12 years of age or older with newly diagnosed, advanced-stage classic Hodgkin's lymphoma were assigned to receive N+AVD or BV+AVD for six cycles. Radiation therapy directed to residual lesions that were metabolically active after treatment was permitted. The primary end point was progression-free survival.



PATIENTS



WHO	**970 patients 12 years of age or older** **Median age, approximately 27 years** **Men: 56%; Women: 44%**
CLINICAL STATUS	**Stage III or IV classic Hodgkin's lymphoma** **No previous treatment** **Zubrod performance status of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability)** **Adequate hematologic and organ function**

TRIAL DESIGN

- PHASE 3
- OPEN-LABEL
- RANDOMIZED
- LOCATION: 256 SITES IN THE UNITED STATES AND CANADA

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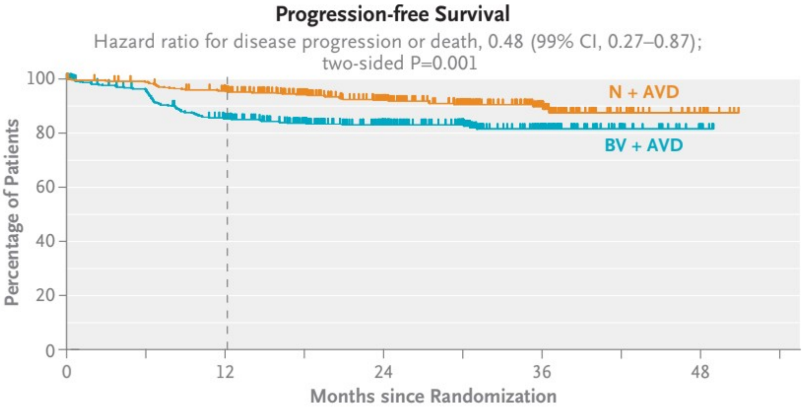
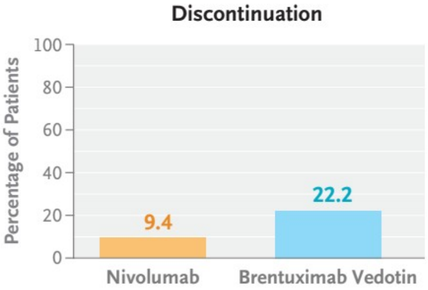
RESULTS

At the prespecified second interim analysis (median follow-up, 12.1 months), progression-free survival was significantly improved with N+AVD as compared with BV+AVD. The improvement with N+AVD was sustained after an additional year of follow-up.

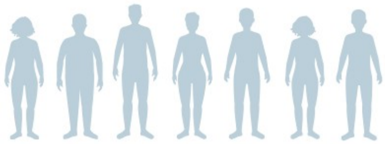

Progression-free Survival

Hazard ratio for disease progression or death, 0.48 (99% CI, 0.27–0.87); two-sided P=0.001


Discontinuation

Fewer patients discontinued nivolumab than brentuximab vedotin. Most treatment discontinuations were due to adverse events.

RADIATION THERAPY



Only seven patients received radiation therapy — three in the N+AVD group and four in the BV+AVD group.

LIMITATIONS AND REMAINING QUESTIONS

- The duration of follow-up was short.
- Secondary analyses and subgroup analyses using specified stratification factors were preplanned, but these analyses did not have adequate statistical power.
- Future research into whether certain biomarkers could help identify patients more likely to benefit from a particular regimen would be appropriate.

CONCLUSIONS

In adolescents and adults with previously untreated, stage III or IV classic Hodgkin's lymphoma, N+AVD improved progression-free survival, as compared with BV+AVD, and had a better side-effect profile.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03907488

Trial funding: National Cancer Institute of the National Institutes of Health and others

Full citation: Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+AVD in advanced-stage classic Hodgkin's lymphoma. N Engl J Med 2024;391:1379-89. DOI: 10.1056/NEJMoa2405888

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EDITORIAL

Therapy for Hodgkin's Lymphoma — Can It Get Any Better?

James O. Armitage, M.D., and Dan L. Longo, M.D.

The approach to Hodgkin's lymphoma treatment has emphasized the use of chemotherapy agents and radiation therapy to kill cancer cells. In the past, radiation therapy was able to cure some patients with limited-stage Hodgkin's lymphoma, but most patients continued to die of the disease.

However, the publication of results regarding the MOPP regimen (mechlorethamine, vincristine, procarbazine, and prednisone) in 1970[1] led to a dramatic reduction in deaths from this lymphoma in the United States over the ensuing decade. The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) was introduced in 1975,[2] and subsequent studies showed it to be more effective than MOPP, with delayed toxic effects occurring in fewer patients.[3] Other studies of very intensive regimens (e.g., BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone][4]) showed somewhat higher rates of complete remission, but greater numbers of deaths from early and late toxic effects made these therapies more difficult to administer and compromised any survival advantage.[5]

At this point, the field seemed to have plateaued. However, insights in the field of cancer biology identified other potential approaches to cancer treatment in general and Hodgkin's lymphoma in particular. Two notable examples are targets of immunotherapy approaches, CD30 and programmed death ligand 1 (PD-L1).

An anti-CD30 antibody was used as the targeting moiety for an antibody–drug conjugate, brentuximab vedotin, and its potent antitumor effects were documented in a number of studies of Hodgkin's lymphoma and other CD30-positive cancers.[6] The ECHELON-1 trial, first published in 2018[7] and updated in 2022,[8] compared the standard regimen, ABVD, with a new regimen in which the anti-CD30 brentuximab vedotin replaced bleomycin to produce BV+AVD. Bleomycin was left out of the chemotherapy regimen because brentuximab vedotin and bleomycin may each cause interstitial pneumonitis, and investigators concluded that it would be wise to avoid including agents with overlapping toxic effects, although the neurotoxic effects associated with both brentuximab vedotin and vinblastine also posed a potential problem. Going after Hodgkin's lymphoma by attacking CD30 made sense because the expression of CD30 on Reed–Sternberg cells is high. After a median follow-up of 6 years, progression-free survival with ABVD therapy was nearly 75% and with BV+AVD was 82.3% (hazard ratio for disease progression or death, 0.68). Overall survival was also better: 89.4% with ABVD and 93.9% with BV+AVD (hazard ratio for death, 0.59).

When the results of treatment are this good, improving on them is a very difficult task. The number of patients that are needed to show that a therapy is more effective becomes unachievable as success rates start to approach and exceed 9 of 10. The task is even more daunting with a relatively rare tumor such as Hodgkin's lymphoma, which is diagnosed in fewer than 9000 people each year in the United States. This difficulty has led to a trend toward focusing on reducing the duration and intensity of treatment to reduce toxic effects without compromising antitumor efficacy. Many investigators assumed that the antitumor effects that were possible with therapy had probably been maximized. However, the Southwest Oncology Group S1826 trial, reported by Herrera et al. in this issue of the *Journal*,[9] undermines that assumption.

The rationale for incorporating immune checkpoint blockade into primary treatment is well founded. PD-L1 is highly expressed on Reed–Sternberg cells,[10] owing in part to selective 9p24.1 amplification in those cells. Clinical testing showed that blocking the interaction between PD-L1 on Reed–Sternberg cells and programmed death 1 (PD-1), its target on lymphocytes, with an antibody to PD-1 resulted in a very high level of antitumor activity in patients with relapsed Hodgkin's lymphoma that was refractory to chemotherapy, presumably related to the distinctive immune mechanism of action of anti–PD-1.[11] Brentuximab vedotin cytotoxicity is chemotherapy-based, and mechanisms that lead to resistance to other microtubule poisons are likely to show cross-resistance to brentuximab vedotin. In addition, cells can still avert the immunotoxin toxicity by down-regulating CD30 expression. In contrast, resistance mechanisms to immune cellular cytotoxicity are not well defined, and it is possible that cells maintain vulnerability to immune attack longer than they do their susceptibility to chemotherapy.

The S1826 trial was designed to assess the efficacy of brentuximab vedotin as compared with nivolumab when combined with the same active chemotherapy. Nearly 1000 patients underwent randomization for the trial. The follow-up was relatively short, but the 2-year progression-free survival was 92% (95% confidence interval [CI], 89 to 94) with nivolumab plus AVD (N+AVD), as compared with 83% (95% CI, 79 to 86) with BV+AVD (hazard ratio for disease progression or death, 0.45; 95% CI, 0.30 to 0.65). The outcome from treatment with BV+AVD was similar to that seen in the trial comparing ABVD and BV+AVD.[8] The majority of patients with Hodgkin's lymphoma who relapse do so in the first 2 years after treatment; unless remissions induced by immune checkpoint blockade plus chemotherapy are different from those induced by chemotherapy alone, late relapses would be unexpected. However, time will tell. At this point, only 7 patients in the nivolumab group and 14 in the brentuximab vedotin group have died.

Another perhaps unexpected result was the superior treatment outcome seen in older patients who received N+AVD. Hodgkin's lymphoma in patients older than 60 years of age has been associated with a much poorer treatment outcome than that seen in younger patients. However, the 2-year progression-free survival in this age group of 88% with N+AVD, as compared with 65% with BV+AVD (hazard ratio for disease progression or death, 0.30), is probably the best ever reported.

In addition to superior treatment outcomes, several other features strongly favor nivolumab over brentuximab vedotin, including a lower frequency of toxic effects (particularly neurologic toxic effects), bone pain, and abdominal symptoms. Only neutropenia was more common in the N+AVD group than in the BV+AVD group, probably in part related to the mandated use of granulocyte colony-stimulating factor in patients in the BV+AVD group. No differences were noted in the instances of febrile neutropenia. A small number of patients receiving nivolumab had autoimmune thyroid disease, and one had grade 3 adrenal insufficiency. Observation must continue in order to detect late toxic effects or relapses.

An enormously beneficial outcome of the trial is the preservation of high rates of complete remission with very little use of radiation therapy. A total of seven patients across both groups had residual positivity on positron-emission tomography after treatment, which was addressed with localized radiation therapy.

At this point, the durability of the remissions is uncertain, although no data suggest that the remissions are likely to be less durable than those seen with chemotherapy alone. The nivolumab regimen is easy to deliver, is associated with modest toxic effects, and is highly effective. The role of chemotherapy alone in the treatment of early-stage disease is expanding because of its remarkable efficacy and low risk of late effects. This latest trial suggests that N+AVD may become the treatment of choice for all stages of Hodgkin's lymphoma.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND

Steroidal mineralocorticoid receptor antagonists reduce morbidity and mortality among patients with heart failure and reduced ejection fraction, but their efficacy in those with heart failure and mildly reduced or preserved ejection fraction has not been established. Data regarding the efficacy and safety of the nonsteroidal mineralocorticoid receptor antagonist finerenone in patients with heart failure and mildly reduced or preserved ejection fraction are needed.

METHODS

In this international, double-blind trial, we randomly assigned patients with heart failure and a left ventricular ejection fraction of 40% or greater, in a 1:1 ratio, to receive finerenone (at a maximum dose of 20 mg or 40 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of total worsening heart failure events (with an event defined as a first or recurrent unplanned hospitalization or urgent visit for heart failure) and death from cardiovascular causes. The components of the primary outcome and safety were also assessed.

RESULTS

Over a median follow-up of 32 months, 1083 primary-outcome events occurred in 624 of 3003 patients in the finerenone group, and 1283 primary-outcome events occurred in 719 of 2998 patients in the placebo group (rate ratio, 0.84; 95% confidence interval [CI], 0.74 to 0.95; P=0.007). The total number of worsening heart failure events was 842 in the finerenone group and 1024 in the placebo group (rate ratio, 0.82; 95% CI, 0.71 to 0.94; P=0.006). The percentage of patients who died from cardiovascular causes was 8.1% and 8.7%, respectively (hazard ratio, 0.93; 95% CI, 0.78 to 1.11). Finerenone was associated with an increased risk of hyperkalemia and a reduced risk of hypokalemia.

CONCLUSIONS

In patients with heart failure and mildly reduced or preserved ejection fraction, finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo. (Funded by Bayer; FINEARTS-HF ClinicalTrials.gov number, NCT04435626.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Solomon can be contacted at ssolomon@bwh.harvard.edu or at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. Dr. McMurray can be contacted at john.mcmurray@glasgow.ac.uk or at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl., Glasgow G128TA, United Kingdom.

*A list of the committees and investigators in the FINEARTS-HF trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Solomon and McMurray contributed equally to this article.

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The NEW ENGLAND JOURNAL of MEDICINE

Finerenone in Heart Failure with Preserved Ejection Fraction

A PLAIN LANGUAGE SUMMARY

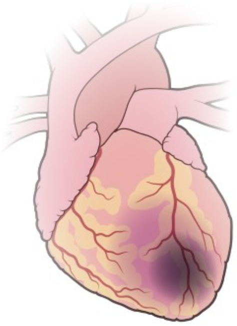
Based on the NEJM publication: Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction
by S.D. Solomon al. (published September 1, 2024)

In this trial, researchers examined the efficacy and safety of finerenone in patients with heart failure with mildly reduced or preserved ejection fraction.

Finerenone is a nonsteroidal mineralocorticoid receptor antagonist. Its physiochemical properties are distinct from those of steroidal mineralocorticoid receptor antagonists, such as spironolactone.

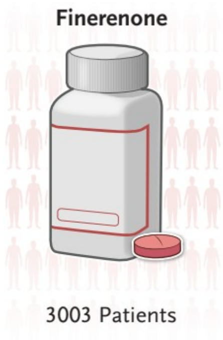
WHY WAS THE TRIAL DONE?

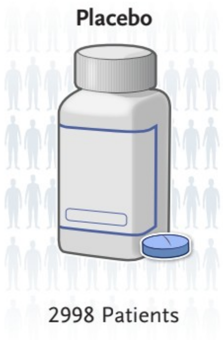
Effective therapies are needed for patients with heart failure and mildly reduced or preserved ejection fraction. Large trials of finerenone have shown a reduced risk of hospitalization for heart failure in patients with chronic kidney disease and diabetes, but studies involving patients with heart failure are needed.



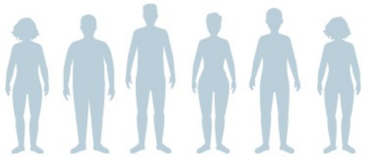
HOW WAS THE TRIAL CONDUCTED?

Adults 40 years of age or older with symptomatic heart failure and mildly reduced or preserved ejection fraction were randomly assigned to receive finerenone (maximum dose, 20 mg or 40 mg once daily) or placebo in addition to their usual therapy. The primary outcome was a composite of total worsening heart failure events and death from cardiovascular causes. A worsening heart failure event was defined as a first or recurrent unplanned hospitalization or urgent visit for heart failure.





PATIENTS



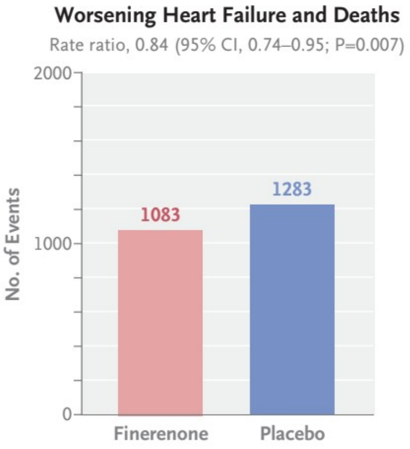
WHO	**6001 patients included in efficacy analysis** **Mean age, 72 years** **Men: 54%; Women: 46%**
CLINICAL STATUS	**Symptomatic heart failure** **Left ventricular ejection fraction of 40% or greater (mean in the trial population, 53%)** **Evidence of structural heart disease** **Elevated levels of natriuretic peptides** **69% of patients in New York Heart Association functional class II**

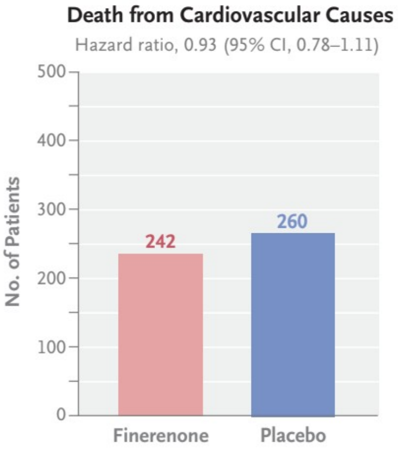
TRIAL DESIGN

- EVENT-DRIVEN
- DOUBLE-BLIND
- RANDOMIZED
- CONTROLLED
- LOCATION: PATIENTS SCREENED AT 654 SITES ACROSS 37 COUNTRIES

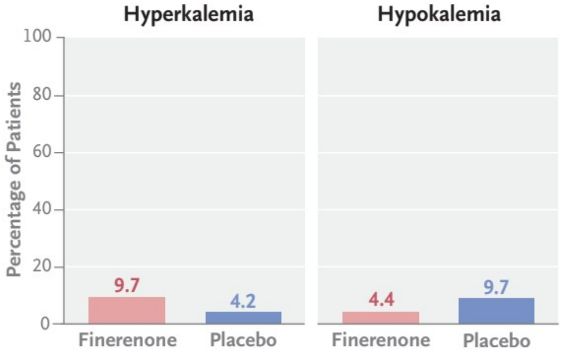
RESULTS

During a median follow-up of 32 months, finerenone resulted in a significantly lower rate of total worsening heart failure events and death from cardiovascular causes than placebo. The rate of worsening heart failure events — a secondary outcome — was also significantly lower with finerenone than with placebo. The percentage of patients who died from cardiovascular causes did not differ substantially between the groups.





Finerenone was associated with a higher risk of hyperkalemia and a lower risk of hypokalemia than placebo.



LIMITATIONS AND REMAINING QUESTIONS

- The trial enrolled few Black patients.
- The observed benefits of finerenone cannot be generalized to other mineralocorticoid receptor antagonists.

CONCLUSIONS

In patients with heart failure and mildly reduced or preserved ejection fraction, finerenone resulted in a significantly lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo.

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04435626

Trial funding: Bayer

Full citation: Solomon SD, McMurray JJV, Vaduganathan M, et al. Finerenone in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2024;391:1475-85. DOI: 10.1056/NEJMoa2407107

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EDITORIAL

FINEARTS-HF — The Latest Masterpiece for MRAs in Heart Failure

Theresa A. McDonagh, M.B., Ch.B., M.D.

Mineralocorticoid receptor antagonists (MRAs) are a cornerstone of treatment for patients with chronic heart failure and reduced ejection fraction. In international guidelines, these agents have a class I recommendation for use in such patients, on the basis of results from seminal trials that showed reductions in death from any cause, death from cardiovascular causes, and hospitalization for heart failure.[1,2] However, their place in the treatment of patients with heart failure and mildly reduced or preserved ejection fraction is less clear. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, which studied the effects of spironolactone as compared with placebo in patients with heart failure and a left ventricular ejection fraction (LVEF) of 45% or greater, did not show a significant reduction in the primary end point — a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.[3] However, results from a subgroup analysis suggested that the risk of the composite outcome was significantly lower with spironolactone than with placebo among patients who had been recruited in the Americas, who had higher cardiovascular risk.[4]

In this issue of the *Journal*, Solomon and colleagues report the results of the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure (FINEARTS-HF).[5] Among the trials of MRAs — and indeed among the trials of renin–angiotensin–aldosterone system inhibitors — for patients with heart failure and an LVEF of 40% or greater, the FINEARTS-HF trial is notable for showing a benefit with respect to its primary end point. In the trial, among the 6016 patients who had undergone randomization, finerenone resulted in a lower rate of a composite of total worsening heart failure events and death from cardiovascular causes than placebo (rate ratio, 0.84; 95% confidence interval, 0.74 to 0.95; P=0.007), with an absolute difference of 2.8 events per 100 patient-years. The chosen primary end point, which was assessed in a total-events analysis, differed from that of previous trials involving patients with heart failure and an LVEF of 40% or greater. However, the results for the more usual end point — a composite of the first worsening heart failure event or death from cardiovascular causes, assessed in a time-to-event analysis — were similar to those for the primary end point. The efficacy of finerenone was evident across subgroups stratified according to the LVEF at baseline, whether mildly reduced or preserved. No heterogeneity in the treatment effect was observed across geographic regions. Finerenone also conferred benefits in the small percentage of patients (14%) who were concomitantly treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors.

When comparing the results from the FINEARTS-HF trial with those from the other two positive trials involving patients with heart failure and an LVEF of 40% or greater, both of which evaluated SGLT2 inhibitors (empagliflozin and dapagliflozin), the overall magnitude of the treatment effect on the primary end point was similar across all three trials.[6,7] In each trial, a significant reduction was observed for heart failure events but not for death from cardiovascular causes. The reason for this pattern is most likely a lack of statistical power. Among patients with heart failure and an LVEF of 40% or greater, the risk of death from any cause is lower than that among patients with heart failure and reduced ejection fraction, and the proportion of deaths that are due to cardiovascular causes is also lower. In the trials evaluating the use of the SGLT2 inhibitors empagliflozin and dapagliflozin in patients with heart failure and an LVEF of 40% or greater, cardiovascular causes accounted for 48% and 55% of the deaths, respectively.[6,7] In the FINEARTS-HF trial, cardiovascular causes accounted for 50% of the deaths, as compared with 87% in the last report from a trial of an MRA for heart failure with reduced ejection fraction.[8] Because the risk of heart failure events decreases as the LVEF increases, trials studying treatments for patients with heart failure and an LVEF of 40% or greater need to be much larger than those studying treatments for patients with systolic heart failure, even when the trial is powered to assess a reduction in a composite outcome. These studies are de facto underpowered to assess a reduction in death from cardiovascular causes.

Unlike spironolactone, finerenone is a nonsteroidal MRA and therefore may be less likely to cause kidney dysfunction and hyperkalemia. In this trial, no treatment effect was seen with respect to a kidney composite end point. However, the trial population had a low risk of kidney events, with a mean estimated glomerular filtration rate of 62 ml per minute per 1.73 m^2 of body-surface area. Finerenone was associated with hyperkalemia: a potassium level greater than 5.5 mmol per liter was observed in 14% of the patients in the finerenone group, and a level greater than 6 mmol per liter was seen in 3%. However, the incidence of hyperkalemia among patients who received finerenone in the FINEARTS-HF trial appeared to be lower than that among patients who received spironolactone in the Americas subgroup of the TOPCAT trial, with a potassium level greater than 5.5 mmol per liter occurring in 24% and a level greater than 6 mmol per liter occurring in 8%.[9]

Given that the FINEARTS-HF trial met its primary end point, the trial results are likely to change the rather weak guideline recommendations for the use of MRAs in patients with chronic heart failure and an LVEF of 40% or greater. Current U.S. and European guidelines give these agents a class IIb recommendation for use in patients with heart failure and mildly reduced ejection fraction, and only the U.S. guidelines give the same recommendation for use in patients with heart failure and preserved ejection fraction. However, while we await new guidelines, this positive trial gives us the option of using finerenone in patients with chronic heart failure and an LVEF of 40% or greater. This treatment option certainly fulfills an unmet need. Currently, only 35% of patients who are hospitalized with heart failure without reduced ejection fraction are discharged while receiving an MRA.[10] The findings also remind us to continue monitoring kidney function and potassium levels in patients treated with finerenone.

Finally, in the broader context of clinical trials of MRAs for chronic heart failure, the FINEARTS-HF trial helps to complete the picture. MRAs now have proven efficacy across the entire spectrum of chronic heart failure.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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EDITORIAL

NEJM at ESC — Finerenone in Heart Failure for Mildly Reduced or Preserved Ejection Fraction

Authors: Eric J. Rubin, M.D., Ph.D., Jane Leopold, M.D., and Stephen Morrissey, Ph.D.

In this audio interview, Editor-in-Chief Eric Rubin and Deputy Editor Jane Leopold discuss research being presented at the 2024 European Society of Cardiology annual meeting.

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Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer

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ABSTRACT

BACKGROUND

In patients with early-stage triple-negative breast cancer, the phase 3 KEYNOTE-522 trial showed significant improvements in pathological complete response and event-free survival with the addition of pembrolizumab to platinum-containing chemotherapy. Here we report the final results for overall survival.

METHODS

We randomly assigned, in a 2:1 ratio, patients with previously untreated stage II or III triple-negative breast cancer to receive neoadjuvant therapy with four cycles of pembrolizumab (at a dose of 200 mg) or placebo every 3 weeks plus paclitaxel and carboplatin, followed by four cycles of pembrolizumab or placebo plus doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide. After definitive surgery, patients received adjuvant pembrolizumab (pembrolizumab–chemotherapy group) or placebo (placebo–chemotherapy group) every 3 weeks for up to nine cycles. The primary end points were pathological complete response and event-free survival. Overall survival was a secondary end point.

RESULTS

Of the 1174 patients who underwent randomization, 784 were assigned to the pembrolizumab–chemotherapy group and 390 to the placebo–chemotherapy group. At the data-cutoff date (March 22, 2024), the median follow-up was 75.1 months (range, 65.9 to 84.0). The estimated overall survival at 60 months was 86.6% (95% confidence interval [CI], 84.0 to 88.8) in the pembrolizumab–chemotherapy group, as compared with 81.7% (95% CI, 77.5 to 85.2) in the placebo–chemotherapy group (P=0.002). Adverse events were consistent with the established safety profiles of pembrolizumab and chemotherapy.

CONCLUSIONS

Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab resulted in a significant improvement, as compared with neoadjuvant chemotherapy alone, in overall survival among patients with early-stage triple-negative breast cancer. (Funded by Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]; KEYNOTE-522 ClinicalTrials.gov number, NCT03036488.)

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*The complete list of principal investigators in the KEYNOTE-522 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 15, 2024, at NEJM.org.

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DOI: 10.1056/NEJMoa2409932

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The NEW ENGLAND JOURNAL of MEDICINE

Overall Survival with Pembrolizumab in Breast Cancer

A PLAIN LANGUAGE SUMMARY

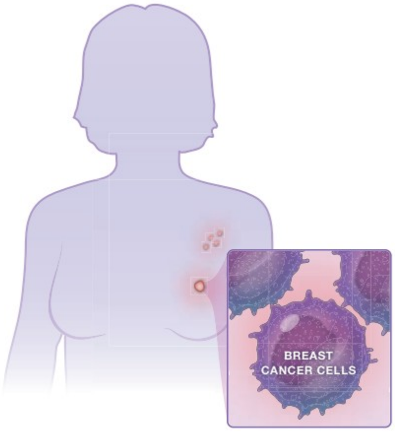
Based on the NEJM publication: Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer by P. Schmid et al. (published September 15, 2024)

In this trial, researchers assessed the efficacy and safety of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab — as compared with neoadjuvant chemotherapy alone — in patients with early-stage triple-negative breast cancer.

Triple-negative breast cancer lacks expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2.

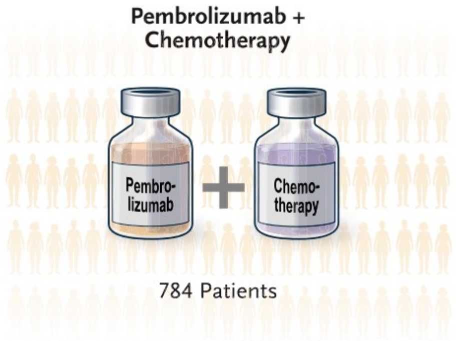
WHY WAS THE TRIAL DONE?

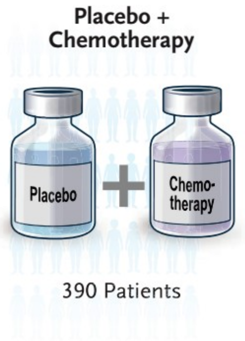
Treatment of triple-negative breast cancer has traditionally been challenging because of the lack of therapeutic targets. The programmed death 1 inhibitor pembrolizumab is approved for early-stage disease on the basis of findings from the KEYNOTE-522 trial, in which neoadjuvant and adjuvant pembrolizumab resulted in improvements in pathological complete response and event-free survival. The findings on overall survival, a key secondary end point, are now reported.



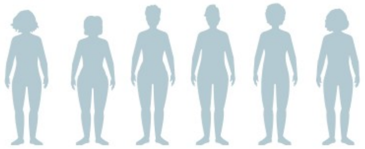
HOW WAS THE TRIAL CONDUCTED?

Patients were assigned, in a 2:1 ratio, to a pembrolizumab–chemotherapy group or a placebo–chemotherapy group. In the neoadjuvant phase, patients received pembrolizumab or placebo for four cycles plus paclitaxel and carboplatin, followed by pembrolizumab or placebo for four cycles plus doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide. After definitive surgery, patients received adjuvant pembrolizumab or placebo for up to nine cycles.





PATIENTS



WHO	**1174 adults**
	Median age: 49 years (pembrolizumab–chemotherapy group) and 48 years (placebo–chemotherapy group)
	Women: 99.9%; Men: 0.1%
CLINICAL STATUS	**Stage II or III triple-negative breast cancer**
	No previous treatment
	Eastern Cooperative Oncology Group performance-status score, 0 or 1 (range, 0 to 5, with higher scores indicating greater disability)

TRIAL DESIGN

- PHASE 3
- DOUBLE-BLIND
- RANDOMIZED
- PLACEBO-CONTROLLED
- LOCATION: 181 SITES IN 21 COUNTRIES

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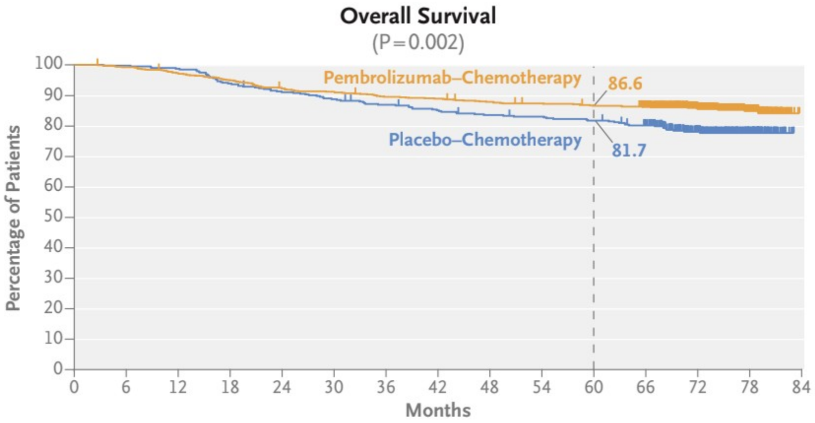
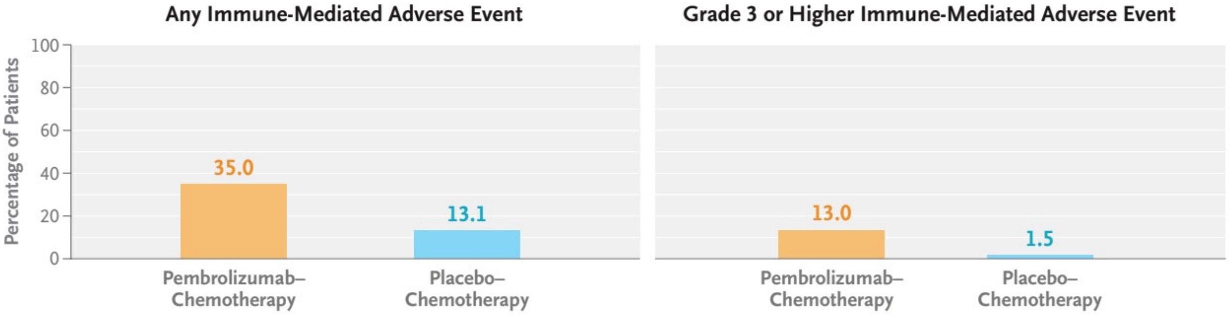
RESULTS

Median follow-up was 75.1 months. Estimated overall survival at 60 months was higher in the pembrolizumab–chemotherapy group than in the placebo–chemotherapy group.

Adverse events were similar to those reported in previous analyses. As expected, immune-mediated adverse events occurred more frequently with pembrolizumab–chemotherapy.





LIMITATIONS AND REMAINING QUESTIONS

- The trial was not designed to discern the relative efficacy contributions of the neoadjuvant and adjuvant treatment phases.
- Trial results showing a survival benefit with capecitabine in triple-negative breast cancer had not yet been reported at the time this trial was designed, so adjuvant capecitabine was not included in the treatment protocol.
- Analyses of molecular biomarkers that might predict clinical response to pembrolizumab are ongoing.

CONCLUSIONS

In patients with early-stage triple-negative breast cancer, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab improved overall survival as compared with neoadjuvant chemotherapy alone.

LINKS: **FULL ARTICLE** | **NEJM QUICK TAKE** | **EDITORIAL**

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT03036488

Trial funding: Merck Sharp and Dohme, a subsidiary of Merck

Full citation: Schmid P, Cortes J, Dent R, et al. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. N Engl J Med 2024;391:1981-91. DOI: 10.1056/NEJMoa2409932

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EDITORIAL

Immunotherapy for Early-Stage Triple-Negative Breast Cancer

Harold J. Burstein, M.D., Ph.D.

Early-stage triple-negative breast cancers, which lack expression of three proteins (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2), have long been defined by what they are not. Now they have found a new identity and treatment approach: they are breast cancers that benefit from immune checkpoint inhibitor therapy. Triple-negative breast cancer is characterized by higher tumor expression of the immunomodulatory protein programmed death ligand 1 (PD-L1), greater tumor mutational burden, and more extensive tumor-infiltrating lymphocytes than other breast cancer subtypes — all of which suggested potential benefit from immunotherapy. The survival data from the KEYNOTE-522 trial that are reported in this issue of the *Journal*[1] are a major validation of that hypothesis.

In the trial, women with stage II or III triple-negative breast cancer were randomly assigned to receive neoadjuvant (preoperative) chemotherapy alone or neoadjuvant chemotherapy with pembrolizumab, which blocks the programmed death 1 receptor on T cells from inhibitory signals delivered by PD-L1 binding. Previous reports from the KEYNOTE-522 trial had shown that adding pembrolizumab increased the likelihood of pathological complete response (eradication of tumor in the breast and axillary lymph nodes) as compared with chemotherapy treatment alone and decreased the likelihood of breast cancer recurrence.[2] The new data show that at 5 years, pembrolizumab improved overall survival by 5 percentage points, from 82% to 87%. The similar GeparNuevo trial, which randomly assigned patients with early-stage triple-negative breast cancer to receive neoadjuvant chemotherapy with or without the checkpoint inhibitor durvalumab, also showed improvement in pathological complete response, recurrence-free survival, and overall survival with combination chemoimmunotherapy.[3]

Gains in survival, as opposed to other end points such as pathological complete response or even recurrence, matter crucially to patients with early-stage triple-negative breast cancer, many of whom will do well with conventional treatments and all of whom will endure more side effects with immunotherapy. The KEYNOTE-522 trial deployed a “maximalist,” four-drug chemotherapy backbone that involved a longer treatment program with more fatigue, cytopenias, treatment interruptions, and short-term side effects than other chemotherapy regimens. The addition of pembrolizumab modestly diminishes near-term quality of life; causes unique, immune-related toxic effects, including thyroid or adrenal disorders that may warrant lifelong treatment; and can rarely induce serious colitis, pneumonitis, hepatitis, or other autoimmune reactions.[1,2]

The demonstration of a survival benefit is also critical in early-stage triple-negative breast cancer because pathological complete response is an imperfect surrogate measure of later outcomes. When neoadjuvant therapy yields a pathological complete response, the patient has a far lower risk of recurrence. Biomarkers such as PD-L1 expression or tumor-infiltrating lymphocytes are associated with a higher likelihood of pathological complete response after either neoadjuvant chemotherapy or chemoimmunotherapy.[2,4,5] The easy measurability of pathological complete response makes it a favored end point for many clinical trials. Intriguingly, in the KEYNOTE-522 and GeparNuevo trials, benefit with checkpoint inhibition was seen regardless of PD-L1 expression, but more importantly, pathological complete response did not capture the full magnitude of survival benefit from adding immunotherapy. Substantial benefits in recurrence and survival were seen among the cohort with residual cancer despite chemoimmunotherapy, whereas patients who had a pathological complete response with either chemotherapy alone or chemoimmunotherapy had roughly similar survival.[1,3,6] Thus, contrary to many clinical-trial assumptions, using pathological complete response as a surrogate end point for outcomes in early-stage triple-negative breast cancer may be insufficient for appreciating the full effect on recurrence or survival in patients receiving checkpoint inhibitor therapy.

Historically, neoadjuvant chemotherapy has yielded survival equivalent to that with adjuvant (postoperative) treatment, with the clinical advantage of tumor downstaging before surgery.[7] With immune checkpoint inhibitor treatment, however, the outcome is different. Neoadjuvant chemoimmunotherapy induced survival gains, whereas adjuvant checkpoint inhibitor treatment has not.[8,9] These findings may reflect the importance of intact tumor–immune interactions for generating maximal treatment effect. Regardless, the fact that neoadjuvant and adjuvant treatment outcomes are not equivalent overturns the major tenet of neoadjuvant treatment and establishes neoadjuvant chemoimmunotherapy as a vital first step for improving outcomes that, to date, cannot be obtained in the adjuvant context.

This new chemoimmunotherapy strategy in early-stage triple-negative breast cancer inevitably poses many questions.[10] Is the four-drug chemotherapy backbone essential, or could anthracyclines or one of the other chemotherapy agents be omitted? Might antibody–drug conjugates replace chemotherapy? How necessary is the "adjuvant" phase of checkpoint inhibitor treatment — administered in the KEYNOTE-522 trial but not in the GeparNuevo trial? Can clinical or biologic markers spare patients immunotherapy, or chemotherapy, in lower-risk cases? Will newer immunotherapies improve outcomes? Would serial measurement of circulating tumor DNA facilitate response-tailored treatment? What prevents immune-related side effects? How should we care for patients undergoing initial surgery for early-stage triple-negative breast cancer but who are subsequently found to have higher-stage cancer than anticipated? Do smaller, stage 1 tumors warrant neoadjuvant chemoimmunotherapy? Arguably, the top priority is improving outcomes for patients with residual cancer despite neoadjuvant chemoimmunotherapy, a group at unacceptably high risk for recurrence. But one question is answered: early-stage triple-negative breast cancer has an identity that is defined by what it needs, not what it lacks.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From Dana–Farber Cancer Institute, Harvard Medical School, Boston.

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EDITORIAL

NEJM at ESMO — Overall Survival with Pembrolizumab in Early-Stage Triple- Negative Breast Cancer

Authors: Eric J. Rubin, M.D., Ph.D., Oladapo O. Yeku, M.D., Ph.D. and Stephen Morrissey, Ph.D.

In this audio interview, Editor-in-Chief Eric Rubin and NEJM Evidence Associate Editor Oladapo Yeku discuss research being presented at the 2024 European Society of Medical Oncology annual meeting.

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DOI: 10.1056/NEJMe2411492

Audio is available at NEJM.org

ORIGINAL ARTICLE

Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

M. Fontana, J.L. Berk, J.D. Gillmore, R.M. Witteles, M. Grogan, B. Drachman, T. Damy, P. Garcia-Pavia, J. Taubel, S.D. Solomon, F.H. Sheikh, N. Tahara, J. González-Costello, K. Tsujita, C. Morbach, Z. Pozsonyi, M.C. Petrie, D. Delgado, P. Van der Meer, A. Jabbour, A. Bondue, D. Kim, O. Azevedo, S. Hvitfeldt Poulsen, A. Yilmaz, E.A. Jankowska, V. Algalarrondo, A. Slugg, P.P. Garg, K.L. Boyle, E. Yureneva, N. Silliman, L. Yang, J. Chen, S.A. Eraly, J. Vest, and M.S. Maurer, for the HELIOS-B Trial Investigators*

ABSTRACT

BACKGROUND

Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, fatal disease. Vutrisiran, a subcutaneously administered RNA interference therapeutic agent, inhibits the production of hepatic transthyretin.

METHODS

In this double-blind, randomized trial, we assigned patients with ATTR-CM in a 1:1 ratio to receive vutrisiran (25 mg) or placebo every 12 weeks for up to 36 months. The primary end point was a composite of death from any cause and recurrent cardiovascular events. Secondary end points included death from any cause, the change from baseline in the distance covered on the 6-minute walk test, and the change from baseline in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score. The efficacy end points were assessed in the overall population and in the monotherapy population (the patients who were not receiving tafamidis at baseline) and were tested hierarchically.

RESULTS

A total of 655 patients underwent randomization; 326 were assigned to receive vutrisiran and 329 to receive placebo. Vutrisiran treatment led to a lower risk of death from any cause and recurrent cardiovascular events than placebo (hazard ratio in the overall population, 0.72; 95% confidence interval [CI], 0.56 to 0.93; $P=0.01$; hazard ratio in the monotherapy population, 0.67; 95% CI, 0.49 to 0.93; $P=0.02$) and a lower risk of death from any cause through 42 months (hazard ratio in the overall population, 0.65; 95% CI, 0.46 to 0.90; $P=0.01$). Among the patients in the overall population, 125 in the vutrisiran group and 159 in the placebo group had at least one primary end-point event. In the overall population, treatment with vutrisiran resulted in less of a decline in the distance covered on the 6-minute walk test than placebo (least-squares mean difference, 26.5 m; 95% CI, 13.4 to 39.6; $P<0.001$) and less of a decline in the KCCQ-OS score (least-squares mean difference, 5.8 points; 95% CI, 2.4 to 9.2; $P<0.001$). Similar benefits were observed in the monotherapy population. The incidence of adverse events was similar in the two groups (99% in the vutrisiran group and 98% in the placebo group); serious adverse events occurred in 62% of the patients in the vutrisiran group and in 67% of those in the placebo group.

CONCLUSIONS

Among patients with ATTR-CM, treatment with vutrisiran led to a lower risk of death from any cause and cardiovascular events than placebo and preserved functional capacity and quality of life. (Funded by Alnylam Pharmaceuticals; HELIOS-B ClinicalTrials.gov number, NCT04153149.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Fontana can be contacted at marianna.fontana@nhs.net or at the National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Hospital, Pond St., London NW3 2QG, United Kingdom.

*A complete list of the HELIOS-B trial investigators and collaborators is provided in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

Ponsegromab for the Treatment of Cancer Cachexia

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Susie M. Collins, M.Sc., Shannon Lubaczewski, Pharm.D., Eric J. Roeland, M.D.,
Tateaki Naito, M.D., Andrew E. Hendifar, M.D., Marie Fallon, M.D.,
Koichi Takayama, M.D., Timothy Asmis, M.D., Richard F. Dunne, M.D.,
Isik Karahanoglu, Ph.D., Carrie A. Northcott, Ph.D., Magdalena A. Harrington, Ph.D.,
Michelle Rossulek, M.A., Ruolun Qiu, Ph.D., and Aditi R. Saxena, M.D.

ABSTRACT

BACKGROUND

Cachexia is a common complication of cancer and is associated with an increased risk of death. The level of growth differentiation factor 15 (GDF-15), a circulating cytokine, is elevated in cancer cachexia. In a small, open-label, phase 1b study involving patients with cancer cachexia, ponsegromab, a humanized monoclonal antibody inhibiting GDF-15, was associated with improved weight, appetite, and physical activity, along with suppressed serum GDF-15 levels.

METHODS

In this phase 2, randomized, double-blind, 12-week trial, we assigned patients with cancer cachexia and an elevated serum GDF-15 level (≥1500 pg per milliliter) in a 1:1:1:1 ratio to receive ponsegromab at a dose of 100 mg, 200 mg, or 400 mg or to receive placebo, administered subcutaneously every 4 weeks for three doses. The primary end point was the change from baseline in body weight at 12 weeks. Key secondary end points were appetite and cachexia symptoms, digital measures of physical activity, and safety.

RESULTS

A total of 187 patients underwent randomization. Of these patients, 40% had non–small-cell lung cancer, 32% had pancreatic cancer, and 29% had colorectal cancer. At 12 weeks, patients in the ponsegromab groups had significantly greater weight gain than those in the placebo group, with a median between-group difference of 1.22 kg (95% credible interval, 0.37 to 2.25) in the 100-mg group, 1.92 (95% credible interval, 0.92 to 2.97) in the 200-mg group, and 2.81 (95% credible interval, 1.55 to 4.08) in the 400-mg group. Improvements were observed across measures of appetite and cachexia symptoms, along with physical activity, in the 400-mg ponsegromab group relative to placebo. Adverse events of any cause were reported in 70% of the patients in the ponsegromab group and in 80% of those in the placebo group.

CONCLUSIONS

Among patients with cancer cachexia and elevated GDF-15 levels, the inhibition of GDF-15 with ponsegromab resulted in increased weight gain and overall activity level and reduced cachexia symptoms, findings that confirmed the role of GDF-15 as a driver of cachexia. (Funded by Pfizer; ClinicalTrials.gov number, NCT05546476.)

From the Internal Medicine Research Unit (J.D.G., I.K., M.A.H., A.R.S.) and Clinical Pharmacology (R.Q.), Pfizer, Cambridge, MA; Duke Cancer Institute, Duke University Medical Center, Durham, NC (J.C.); Global Biometrics and Data Management, Pfizer R&D UK, Sandwich (S.M.C.), and Edinburgh Cancer Research Centre, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh (M.F.) — both in the United Kingdom; Translational Clinical Sciences, Pfizer, Collegeville, PA (S.L.); Knight Cancer Institute, Oregon Health and Science University, Portland (E.J.R.); the Cancer Supportive Care Center, Shizuoka Cancer Center, Shizuoka (T.N.), and the Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine, Kyoto (K.T.) — both in Japan; Cedars–Sinai Medical Center, Los Angeles (A.E.H.); the Ottawa Hospital Cancer Centre, Ottawa (T.A.); Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY (R.F.D.); Translational Clinical Sciences, Pfizer, Groton, CT (C.A.N.); and the Internal Medicine Research Unit, Pfizer, Tampa, FL (M.R.). Dr. Groarke can be contacted at john.groarke@pfizer.com or at the Pfizer Internal Medicine Research Unit, KSQ1-004, 1 Portland St., Cambridge, MA 02139.

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EDITORIAL

NEJM at ESMO — Ponsegromab in Cancer Cachexia

Authors: Eric J. Rubin, M.D., Ph.D., Oladapo O. Yeku, M.D., Ph.D. and Stephen Morrissey, Ph.D.

In this audio interview, Editor-in-Chief Eric Rubin and NEJM Evidence Associate Editor Oladapo Yeku discuss research being presented at the 2024 European Society of Medical Oncology annual meeting.

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ORIGINAL ARTICLE

CRISPR-Based Therapy for Hereditary Angioedema

Danny M. Cohn, M.D., Ph.D., Padmalal Gurugama, M.D., Markus Magerl, M.D., Constance H. Katelaris, M.B., B.S., Ph.D., F.R.A.C.P., David Launay, M.D., Ph.D., Laurence Bouillet, M.D., Ph.D., Remy S. Petersen, M.D., Karen Lindsay, M.B., Ch.B., Emel Aygören-Pürsün, M.D., David Maag, Ph.D., James S. Butler, Ph.D., Mrinal Y. Shah, Ph.D., Adele Golden, Ph.D., Yuanxin Xu, M.D., Ph.D., Ahmed M. Abdelhady, Ph.D., David Lebwohl, M.D., and Hilary J. Longhurst, Ph.D., F.R.A.C.P.

ABSTRACT

BACKGROUND

Hereditary angioedema is a rare genetic disease characterized by severe and unpredictable swelling attacks. NTLA-2002 is an in vivo gene-editing therapy that is based on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9. NTLA-2002 targets the gene encoding kallikrein B1 (*KLKB1*). A single dose of NTLA-2002 may provide lifelong control of angioedema attacks.

METHODS

In this phase 2 portion of a phase 1–2 trial, we randomly assigned adults with hereditary angioedema in a 2:2:1 ratio to receive NTLA-2002 in a single dose of 25 mg or 50 mg or placebo. The primary end point was the number of angioedema attacks per month (the monthly attack rate) from week 1 through week 16. Secondary end points included safety, pharmacokinetics, and pharmacodynamics (i.e., the change from baseline in total plasma kallikrein protein level); exploratory end points included patient-reported outcomes.

RESULTS

Of the 27 patients who underwent randomization, 10 received 25 mg of NTLA-2002, 11 received 50 mg, and 6 received placebo. From week 1 through week 16, the estimated mean monthly attack rate was 0.70 (95% confidence interval [CI], 0.25 to 1.98) with 25 mg of NTLA-2002, 0.65 (95% CI, 0.24 to 1.76) with 50 mg, and 2.82 (95% CI, 0.80 to 9.89) with placebo; the difference in the estimated mean attack rate with NTLA-2002 as compared with placebo was −75% with 25 mg and −77% with 50 mg. Among patients who received NTLA-2002, 4 of the 10 patients who received 25 mg (40%) and 8 of the 11 who received 50 mg (73%) were attack-free with no additional treatment during the period from week 1 through week 16. The most common adverse events among patients who received NTLA-2002 were headache, fatigue, and nasopharyngitis. The mean percent change in total plasma kallikrein protein levels from baseline to week 16 was −55% with 25 mg and −86% with 50 mg; levels remained unchanged with placebo.

CONCLUSIONS

NTLA-2002 administered in a single dose of 25 mg or 50 mg reduced angioedema attacks and led to robust and sustained reduction in total plasma kallikrein levels in patients with hereditary angioedema. These results support continued investigation in a larger phase 3 trial. (Funded by Intellia Therapeutics; ClinicalTrials.gov number, NCT05120830; EudraCT number, 2021-001693-33.)

The authors' affiliations are listed in the Appendix. Dr. Cohn can be contacted at d.m.cohn@amsterdamumc.nl or at Amsterdam University Medical Center, Meibergdreef 9, Amsterdam, 1105 AZ, Netherlands.

A complete list of subprincipal investigators and study-site coordinators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

A Milestone for Gene-Editing Therapies

Kiran Musunuru, M.D., Ph.D.

Are gene-editing therapies actually helping patients? Although there has been considerable excitement about the prospect of directly administering gene-editing therapy that is based on clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 9 (Cas9) into the bodies of patients to treat diseases,[1] we have only recently begun to see signs of success in clinical settings. In an early demonstration of the use of gene-editing therapy, reported in 2021, in vivo liver-directed CRISPR-Cas9 treatment substantially reduced serum transthyretin concentrations in a small number of patients with transthyretin amyloidosis.[2] A report from early 2024 described in vivo CRISPR-Cas9 treatment that targeted the gene *KLKB1* in the liver in a small cohort of patients with hereditary angioedema, with that therapy resulting in large reductions in plasma kallikrein protein levels.[3] A noteworthy aspect of the latter study was a marked decrease in the frequency of angioedema attacks after treatment. This observation was early evidence that in vivo gene editing resulted in improved quality of life. A third study, reported later in 2024, used in vivo CRISPR-Cas9 treatment to target a pathogenic *CEP290* variant in photoreceptor cells in a small number of patients with inherited retinal degeneration; the results were somewhat ambiguous, with only a subgroup of the patients having visual improvements as assessed by various metrics.[4] None of these studies had a control group, which raises the specter of placebo effects accounting for some of the changes.

Cohn et al. now provide in the *Journal* evidence from a randomized, controlled trial that a gene-editing therapy has resulted in clinical benefit.[5] They report the phase 2 portion of a phase 1–2 trial, the phase 1 portion of which was the aforementioned study of *KLKB1*-editing in patients with hereditary angioedema, with the therapy designated NTLA-2002.[3] Whereas the phase 1 study included 10 patients divided among three dose groups (25 mg, 50 mg, and 75 mg of NTLA-2002), the phase 2 trial randomly assigned 27 patients to one of two dose groups (25 mg or 50 mg) or a placebo group. The phase 2 cohort was still relatively small and the number of patients was not balanced among the groups (with 6 patients receiving placebo as compared with 10 receiving 25 mg of NTLA-2002 and 11 receiving 50 mg), factors that limit the ability to perform statistical comparisons, but the results were nonetheless revealing. During the 16-week primary observation period after treatment, the patients who received 25 mg of NTLA-2002 had a 75% reduction in the number of angioedema attacks per month (the monthly attack rate) as compared with the patients who received placebo, and the group that received 50 mg had a 77% reduction.

Besides confirming the clinical benefit of treatment with NTLA-2002, the phase 2 trial shows the importance of larger randomized, controlled trials for clarifying the magnitude of clinical benefit. The results of the phase 1 study showed an intraindividual reduction from baseline in the monthly attack rate of 91% in the 25-mg group and 97% in the 50-mg group during the 16-week primary observation period[3]; in the phase 2 trial, there was an intraindividual reduction of 16% in the placebo group,[5] a finding that suggests a modest placebo effect in the phase 1 study. Results from a future phase 3 randomized, controlled trial will better inform providers and patients as to the relative benefits of gene-editing therapy as compared with other methods of treatment for hereditary angioedema.

Although the phase 2 trial is the main focus of the article by Cohn et al., the authors have also provided an update on the status of the patients in the phase 1 study.[5] Relative to the initial findings published in early 2024, there is now an additional year of follow-up for the 10 patients in phase 1. During the newly reported follow-up period, there was just one angioedema attack in the entire cohort, even though none of the patients were on long-term prophylaxis during this period. (In the phase 2 trial, the number of angioedema attacks in patients who received NTLA-2002 was higher than that in the phase 1 study, and two patients who received NTLA-2002 have resumed long-term prophylaxis.) It is also notable that during that additional year, the reductions in total plasma kallikrein protein levels observed in all three dose groups of the phase 1 study remained stable, with 2 years of post-treatment data now available for patients in the low-dose (25-mg) group (the first to undergo treatment in the study). The durability of the therapeutic effect shows promise to last for the patients' lifetimes, making the CRISPR-based treatment a truly "one-and-done" proposition.

The answer to the opening question is now an unambiguous "yes." We can be confident that NTLA-2002 is helping patients with hereditary angioedema, and it is only a matter of time before we will see gene-editing treatments having a transformative effect on the care of patients with a broad spectrum of diseases.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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ORIGINAL ARTICLE

Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

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ABSTRACT

BACKGROUND

Obesity increases the risk of heart failure with preserved ejection fraction. Tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, causes considerable weight loss, but data are lacking with respect to its effects on cardiovascular outcomes.

METHODS

In this international, double-blind, randomized, placebo-controlled trial, we randomly assigned, in a 1:1 ratio, 731 patients with heart failure, an ejection fraction of at least 50%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo for at least 52 weeks. The two primary end points were a composite of adjudicated death from cardiovascular causes or a worsening heart-failure event (assessed in a time-to-first-event analysis) and the change from baseline to 52 weeks in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating better quality of life).

RESULTS

A total of 364 patients were assigned to the tirzepatide group and 367 to the placebo group; the median duration of follow-up was 104 weeks. Adjudicated death from cardiovascular causes or a worsening heart-failure event occurred in 36 patients (9.9%) in the tirzepatide group and in 56 patients (15.3%) in the placebo group (hazard ratio, 0.62; 95% confidence interval [CI], 0.41 to 0.95; P=0.026). Worsening heart-failure events occurred in 29 patients (8.0%) in the tirzepatide group and in 52 patients (14.2%) in the placebo group (hazard ratio, 0.54; 95% CI, 0.34 to 0.85), and adjudicated death from cardiovascular causes occurred in 8 patients (2.2%) and 5 patients (1.4%), respectively (hazard ratio, 1.58; 95% CI, 0.52 to 4.83). At 52 weeks, the mean (±SD) change in the KCCQ-CSS was 19.5±1.2 in the tirzepatide group as compared with 12.7±1.3 in the placebo group (between-group difference, 6.9; 95% CI, 3.3 to 10.6; P<0.001). Adverse events (mainly gastrointestinal) leading to discontinuation of the trial drug occurred in 23 patients (6.3%) in the tirzepatide group and in 5 patients (1.4%) in the placebo group.

CONCLUSIONS

Treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo and improved health status in patients with heart failure with preserved ejection fraction and obesity. (Funded by Eli Lilly; SUMMIT ClinicalTrials.gov number, NCT04847557.)

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*A list of the SUMMIT Trial Study Group investigators is provided in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

NEJM at AHA — Tirzepatide for Heart Failure with Preserved Ejection Fraction and Obesity

Authors: Eric J. Rubin, M.D., Ph.D., Jane Leopold, M.D., and Stephen Morrissey, Ph.D.

In this audio interview, Editor-in-Chief Eric Rubin and Deputy Editor Jane Leopold discuss research being presented at the 2024 American Heart Association Scientific Sessions.

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NEJM Evidence

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ORIGINAL ARTICLE

Automated Insulin Delivery for Young People with Type 1 Diabetes and Elevated A1c

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Abstract

BACKGROUND Automated insulin delivery is the treatment of choice in adults with type 1 diabetes. Data are needed on the efficacy and safety of automated insulin delivery for children and youth with diabetes and elevated glycated hemoglobin levels.

METHODS In this multicenter, open-label randomized controlled trial, we assigned patients with type 1 diabetes in a 1:1 ratio either to use an automated insulin delivery system (MiniMed 780G) or to receive usual diabetes care of multiple daily injections or non-automated pump therapy (control). The patients were children and youth (defined as 7 to 25 years of age) with elevated glycemia (glycated hemoglobin ≥8.5% with no upper limit). The primary outcome was the baseline-adjusted between-group difference in glycated hemoglobin at 13 weeks.

RESULTS A total of 80 patients underwent randomization (37 to automated insulin delivery and 43 to control) and all patients completed the trial. At 13 weeks, the mean (±SD) glycated hemoglobin decreased from 10.5±1.9% to 8.1±1.8% in the automated insulin delivery group but remained relatively consistent in the control group, changing from 10.4±1.6% to 10.6±1.8% (baseline-adjusted between-group difference, −2.5 percentage points; 95% confidence interval [CI], −3.1 to −1.8; P<0.001). Patients in the automated insulin delivery group spent on average 8.4 hours more in the target glucose range of 70 to 180 mg/dl than those in the control group. One severe hypoglycemia event and two diabetic ketoacidosis events occurred in the control group, with no such events in the automated insulin delivery group.

CONCLUSIONS In this trial of 80 children and youth with elevated glycated hemoglobin, automated insulin delivery significantly reduced glycated hemoglobin compared with usual diabetes care, without resulting in severe hypoglycemia or diabetic ketoacidosis events. (Funded by Lions Clubs New Zealand District 202F and others; Australian New Zealand Clinical Trials Registry number, ACTRN12622001454763.)

Background

At the age of 20 years, young people with type 1 diabetes face a loss of life expectancy of greater than a decade.[1,2] Maintaining healthy glycemia is paramount for reducing this risk related to long-term microvascular and macrovascular complications.[3,4] However, international data show that less than one fifth of children and youth

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NEJM Evidence

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EDITORIAL

Getting Diabetes Technologies into the Hands of Those Who Need Them Most

Alanna Weisman, M.D., Ph.D.[1,2,3]

Automated insulin delivery is the most advanced technology currently available for the management of type 1 diabetes. Automated insulin delivery systems combine an insulin pump, a continuous glucose monitor, and a mathematical algorithm to automatically adjust insulin delivery based on current and predicted blood glucose levels. Owing to their impressive benefits on both glycemic outcomes and patient-reported outcome measures, such as quality of life, the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes recommend automated insulin delivery for all individuals with type 1 diabetes who are willing and able to use it appropriately.[1,2]

In this issue of *NEJM Evidence*, investigators report the results of the Closed Loop in Children and Youth with Type 1 Diabetes and High-Risk Glycemic Control (CO-PILOT) trial, a 13-week parallel-group randomized controlled trial.[3] For a group of 80 children and young adults with an A1C level equal to or above 8.5%, the impact of using an automated insulin delivery system (specifically Medtronic's MiniMed 780G system) was compared with multiple daily injections or non-automated insulin pump therapy.[3] Among automated insulin delivery users, the levels of A1C were reduced from 10.5 to 8.1% and time spent in the recommended target glucose range increased by 32 percentage points, while these measures were unchanged in the standard care group. Importantly, no safety concerns or adverse events occurred in the automated insulin delivery group.

The CO-PILOT trial is one of the first randomized controlled trials to evaluate automated insulin delivery in a population with high A1C levels, as well as diversity in ethnicity and socioeconomic status. Individuals in these populations have been underrepresented in automated insulin delivery studies previously. A limitation of the generalizability of the CO-PILOT trial was the frequent contact between the trial team and participants. It is unclear if the same glycemic benefits would be observed in clinical practice if frequent contact with patients was not feasible. Additionally, the relatively small sample size of the trial necessitates that the interpretation of safety data be approached with caution.

In previous automated insulin delivery trials for type 1 diabetes, in which mean A1C values were typically around 7.5% at baseline, the use of automated insulin delivery lowered A1C levels by approximately 0.5 percentage points and improved the time spent in the target glucose range by approximately 10 percentage points.[4-6] The CO-PILOT trial emphatically demonstrates that those with high A1C levels (i.e., equal to or above 8.5%) have a substantially greater absolute benefit in terms of glycemic outcomes. Therefore, individuals with high A1C levels are, arguably, the single most important group to prioritize for automated insulin delivery.

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Among individuals with type 1 diabetes, those with higher A1C levels are more likely to be socially disadvantaged (e.g., of a historically marginalized ethnicity, low socioeconomic status, or lacking private insurance).[7] These are the individuals who stand to benefit the most from automated insulin delivery, yet they experience multiple barriers to accessing diabetes technologies. First, financial barriers are a major concern, as diabetes technologies are expensive. Second, insurers or policy makers may limit access to diabetes technologies by enforcing requirements, such as a person's A1C values being below a maximum threshold, the demonstration of a sufficient frequency of blood glucose monitoring, and the completion of education programs. Third, clinicians can intentionally or unintentionally act as "gatekeepers," limiting access to diabetes technologies to only those who they perceive to be good candidates.[8] Clinicians may worry that socially disadvantaged patients do not have the literacy, numeracy, or diabetes self-management skills to successfully and safely use automated insulin delivery.

Diabetes clinics and programs have substantial experience of initiating non-automated insulin pump therapy, and there is an inclination to use similar policies and procedures for initiating automated insulin delivery. However, a paradigm shift is needed. Traditionally, insulin pump initiation has often required patients to provide blood glucose and food logs, as well as demonstrate their ability to accurately count carbohydrates and adjust insulin doses based on blood glucose measurements. Education priorities for automated insulin delivery initiation must shift to the technical skills required to wear and safely manage devices, rather than demonstrate extensive knowledge and skills in glycemic management. Patients who can simply insert and maintain automated insulin delivery devices, as well as prevent and recognize times when insulin delivery by the pump has been interrupted, will do better with automated insulin delivery systems than they would without them, even if they are unable to count carbohydrates and calculate precise insulin doses. Device manufacturers can further reduce barriers by developing automated insulin delivery systems that offer simple meal announcement methods instead of carbohydrate counting and more robust backup methods for when automation is interrupted, such as the device reverting to conservative insulin delivery estimates based on recent data rather than previously programmed insulin rates that may no longer apply for a given patient.

The results of the CO-PILOT trial unequivocally demonstrate the major benefits of automated insulin delivery for individuals with type 1 diabetes who struggle with glycemic management. We must now challenge historical norms and policies by prioritizing the initiation of automated insulin delivery among these individuals, who may not have traditionally been viewed as ideal candidates, ensuring that they can fully benefit from this transformative technology.

Disclosures

Author disclosures are available at evidence.nejm.org.

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ORIGINAL ARTICLE

Towards Generalist Biomedical AI

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Abstract

BACKGROUND Medicine is inherently multimodal, requiring the simultaneous interpretation and integration of insights between many data modalities spanning text, imaging, genomics, and more. Generalist biomedical artificial intelligence systems that flexibly encode, integrate, and interpret these data might better enable impactful applications ranging from scientific discovery to care delivery.

METHODS To catalyze development of these models, we curated MultiMedBench, a new multimodal biomedical benchmark. MultiMedBench encompasses 14 diverse tasks, such as medical question answering, mammography and dermatology image interpretation, radiology report generation and summarization, and genomic variant calling. We then introduced Med-PaLM Multimodal (Med-PaLM M), our proof of concept for a generalist biomedical AI system that flexibly encodes and interprets biomedical data including clinical language, imaging, and genomics with the same set of model weights. To further probe the capabilities and limitations of Med-PaLM M, we conducted a radiologist evaluation of model-generated (and human) chest x-ray reports.

RESULTS We observed encouraging performance across model scales. Med-PaLM M reached performance competitive with or exceeding the state of the art on all MultiMedBench tasks, often surpassing specialist models by a wide margin. In a side-by-side ranking on 246 retrospective chest x-rays, clinicians expressed a pairwise preference for Med-PaLM Multimodal reports over those produced by radiologists in up to 40.50% of cases, suggesting potential clinical utility.

CONCLUSIONS Although considerable work is needed to validate these models in real-world cases and understand if cross-modality generalization is possible, our results represent a milestone toward the development of generalist biomedical artificial intelligence systems. (Funded by Alphabet Inc. and/or a subsidiary thereof.)

Tao Tu and Shekoofeh Azizi contributed equally to this article. Alan Karthikesalingam and Vivek Natarajan jointly supervised this work.

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NEJM Catalyst | Innovations in Care Delivery

IN DEPTH

NYC's Overdose Prevention Centers: Data from the First Year of Supervised Consumption Services

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Unintentional drug overdose deaths are a critical public health concern nationally and locally; New York City (NYC) reported 3,026 overdose fatalities in 2022, the highest number of overdose deaths citywide since reporting began in 2000. The burden of overdose deaths is highly unequal: older New Yorkers, Black and Latino/a New Yorkers, people experiencing homelessness, and residents of high-poverty neighborhoods continue to experience the highest rates of fatal overdose citywide. The rise in overdose deaths is driven by the proliferation of fentanyl, which was present in 81% of overdose deaths in NYC in 2022. Overdose prevention centers (OPCs), also known as supervised consumption spaces, have demonstrated international success in reducing overdose deaths and associated harms. OPCs provide hygienic spaces where people can use previously acquired substances under the supervision of trained staff. These OPCs, which opened in NYC on November 30, 2021, are recognized as the first OPCs with supervised use of illicit substances to be formally supported by a governmental entity in the United States. The OPCs are operated by the nonprofit organization OnPoint NYC; the City of New York provides monetary support for many services at the OPCs except direct supervised consumption, as well technical assistance and programmatic oversight by the NYC Department of Health & Mental Hygiene. This report summarizes the first year of operations of these two centers in NYC. From November 30, 2021, to November 30, 2022,

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